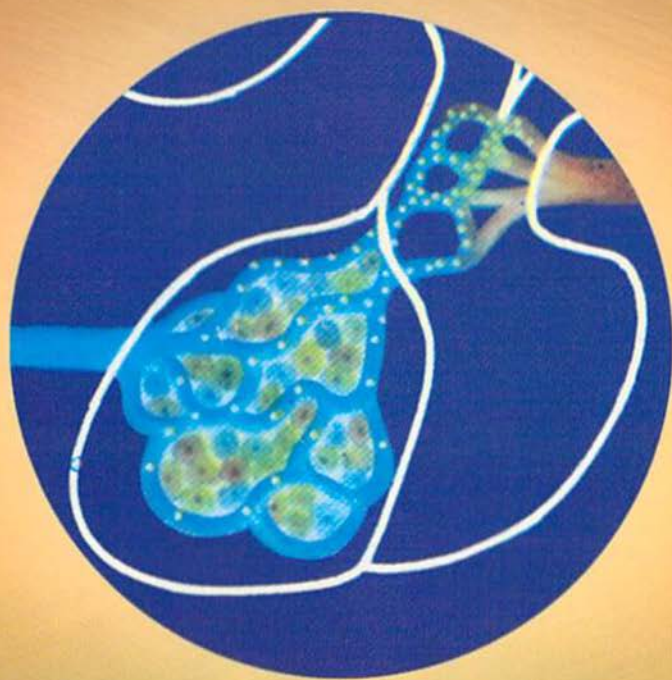


HUMAN

PHYSIOLOGY

For Medical Students



Endocrine Glands and Reproduction

Magdi Sabry M.D

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HUMAN
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FOR MEDICAL STUDENTS

ENDOCRINE GLANDS & REPRODUCTION

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DEDICATED TO

MY TEACHERS THROUGHOUT MY LIFE, particularly the first 2 teachers, my late parents.

MY FAITHFUL LATE WIFE, the light that disappeared from life but is everlasting inside me.

MY SONS, SHERIF, AMR AND ESSAM, AND THEIR WIVES, their love gives me hope and interest in life and makes their happiness my chief goal.

MY GRANDCHILDREN, AHMED, NOURHAN AND SAMA SHERIF, YASMIN AND MOHAMMED AMR, AND AYA ESSAM, the beautiful young angels that have added a new kind of happiness to my life.

PREFACE

With recent advances in the field of human physiology, it has become urgent to provide an up to date review on the subject.

This book is provided to help medical students in understanding modern human physiology. It presents the whole subject in a brief, comprehensive, and up to date form.

Great effort was done to perfect such a vast subject in an easily understandable expression and in a such reasonable bulk. It includes as much simplified and clear illustrations as possible, and to maintain simplicity, they have been presented in a diagrammatic form, photographs were greatly excluded.

The major part of my gratitude should be given to all who taught me, and to my late wife and sons who, patiently, supported me during preparation of this book.

Any suggestions, remarks or criticism will be greatly welcomed, heartily appreciated and very much considered.

I hope this book will be a real help to undergraduate medical students as well as to postgraduates and candidates of higher degrees, in the field of human physiology.

MAGDI SABRY, 1989

Second edition 1994

Third edition 2000

Preface to the fourth edition

This new edition is original both in shape and contents. All chapters have been extensively revised and updated. More figures and illustrations are introduced, and recent data are added elsewhere specially about the mechanisms of action of hormones, and almost all subjects have been completely rewritten.

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SECTION I

ENDOCRINE GLANDS

CHAPTER 1

THE HORMONES

In the human body, there are 2 systems that regulate the functions of other systems. These are **the nervous and the endocrine systems**. The endocrine glands are *ductless glands* that secrete *hormones directly into the bloodstream* through which they reach other sites (= *target organs*) where they exert their actions. They include the following glands (figure 1).

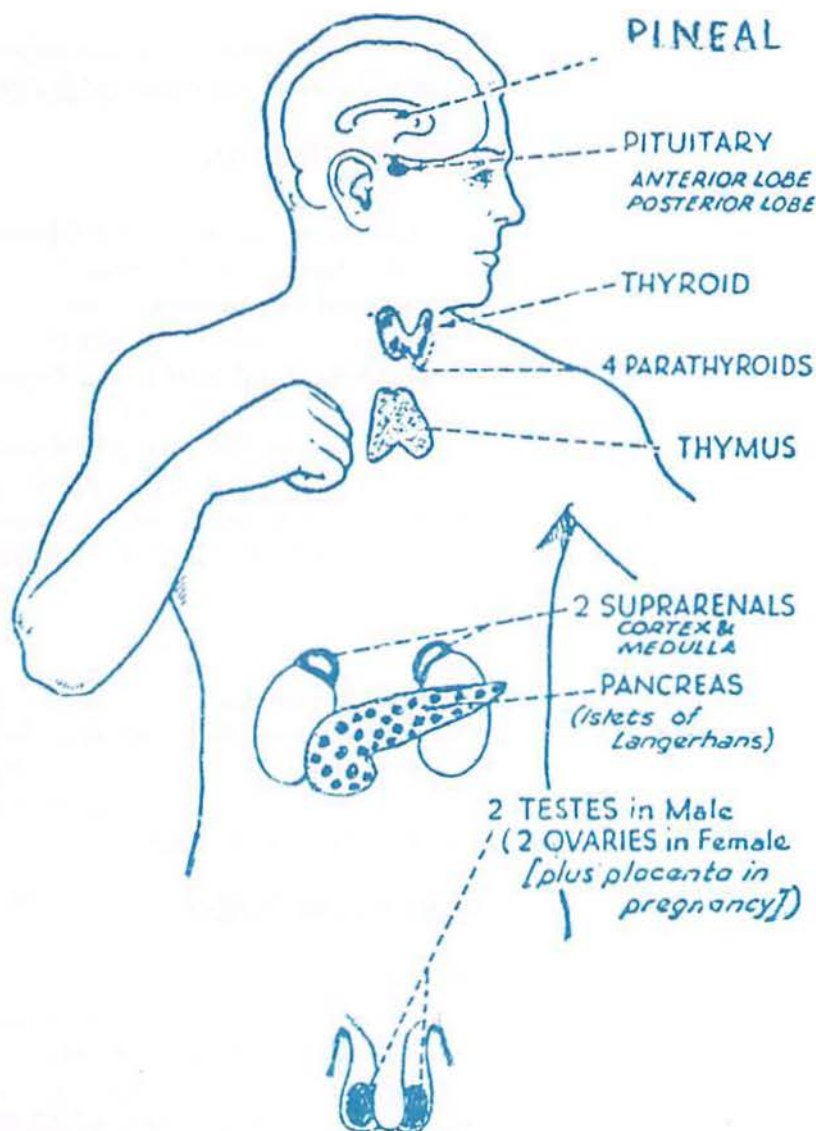


Figure 1 : The human endocrine glands.

Section 1- Chapter 1

Properties of hormones

- (1) Pituitary gland (the hypophysis).
- (2) Thyroid gland.
- (3) Parathyroid glands (usually 4 glands).
- (4) Adrenal (or suprarenal) glands (2 glands, each contains cortex & medulla)
- (5) Sex glands or gonads (2 testes in males and 2 ovaries in females).
- (6) Islets of Langerhans (in the pancreas).
- (7) Pineal gland (the epiphysis).
- (8) Thymus gland (refer to blood).

****** All glands are important for normal body function, but the *anterior pituitary, adrenal cortex and parathyroid glands are essential to life*.

OTHER ENDOCRINE ORGANS

In addition to the endocrine glands mentioned above, the following organs also exert endocrine functions besides their original functions :

1. **The kidneys :** These secrete (a) *Renin* (b) *Erythropoietin* (c) *1,25 –dihydroxycholecalciferol* (the active metabolite of vitamin D₃).
2. **The heart :** The atria secrete *ANP (Atrial Natriuretic Peptide)* which causes natriuretic and hypotensive effects (refer to kidney).
3. **The hypothalamus :** This secretes (a) *The hypophysiotropic hormones*, which affect the activity of the anterior pituitary gland (b) *Antidiuretic hormone (or vasopressin) and oxytocin*, which are stored in then released from the posterior pituitary gland (refer to the pituitary gland).
4. **The placenta** (page 139).
5. **The lungs** (refer to respiration).
6. **The liver** (refer to digestion).

Apart from these "general hormones" secreted by the endocrine glands and the other endocrine organs, there are also "local hormones" that act at (or near) the sites of their secretion. These include (a) *The gastrointestinal hormones* (e.g. gastrin, secretin, CCK, etc.) (b) *The various chemical transmitters released by nerve endings*.

PROPERTIES OF HORMONES

1. They exert *no effects on the glands that secrete them*.
2. Some hormones affect cell activity all over the body (e.g. the growth hormone) while others *act only on specific target cells* (e.g. sex hormones)
3. In the target cells, they trigger (initiate) certain biochemical reactions which *often continue for sometime* after disappearance of the hormones from the bloodstream.

4. Some hormones *exert other effects* in addition to their specific effects e.g. the main action of insulin is to decrease the blood glucose level but, however, it also stimulates protein synthesis (chapter 7).

5. Stimuli that release a certain hormone *inhibit the secretion of other hormones that exert antagonistic effects* e.g. hyperglycemia stimulates insulin secretion and inhibits the secretion of its antagonists (e.g. the growth hormone and glucagon).

6. Normally, hormones are secreted in very small amounts that maintain *a basal quantity of each hormone in the bloodstream*, and the rate of secretion of a certain hormone depends on the needs of the body to this hormone.

7. Many hormones show cyclic variations in their rate of secretion over the 24 hours (= *diurnal or circadian rhythm*) e.g. ACTH and melatonin.

8. Hormones (in contrast to enzymes) are *continuously lost* from the bloodstream by either excretion or metabolic inactivation.

9. Some hormones are secreted in relatively inactive forms then they are *converted in the tissues to more active hormones* (e.g. testosterone and thyroxine).

10. Most hormones circulate in the bloodstream in *2 forms* : A very small amount in the free form, and a *much greater amount bound to plasma proteins*. The free part is the active part capable of exerting effects on the target cells while the bound part acts as a reservoir for the hormone.

CHEMICAL STRUCTURE OF HORMONES

Chemically, the hormones are either *protein or steroid* in nature.

(1) PROTEIN HORMONES : These are classified into 2 groups :

(A) Hormones formed from **one amino acid** : These include

(1) The thyroid hormones i.e. tri-iodothyronine and tetra-iodothyronine (T_3 and T_4) and catecholamines (epinephrine and norepinephrine). All these hormones are derived from the amino acid *tyrosine*.

(2) Melatonin, which is formed from the amino acid *tryptophan*.

(B) Hormones formed of long or short **peptide chains** (= *polypeptide hormones*). These include : (1) All hormones of the anterior and posterior pituitary glands (2) The parathyroid hormone (3) All pancreatic hormones (insulin, glucagon, somatostatin and the PP, chapter 7).

(4) Calcitonin (5) Hypophysiotropic hormones (6) Gastrointestinal hormones (7) Relaxin (8) Inhibin (9) Some placental hormones (e.g. hCG and hCS) (10) Erythropoietin (11) Renin. The later 2, as well as TSH, FSH, LH and hCG are **glycoproteins** (refer to pituitary gland and placenta).

(2) STEROID HORMONES : These are derived from **cholesterol**, and they include (1) All hormones of the adrenal cortex (2) The sex hormones secreted by the male and female gonads (testes and ovaries), the adrenal cortex and the placenta (estrogen and progesterone). (3) 1,25-dihydroxycholecalciferol (the active metabolite of vitamin D₃).

THE HORMONAL RECEPTORS

The hormonal receptors are located either *inside the target cells* (in the cytoplasm or in the nucleus) or on their *membranes*. They are chemically **protein in nature**, and they are **specific** (i.e. each receptor is specified to bind to a certain hormone).

Regulation of hormonal receptors

The hormonal receptors are *not static components of the cell*, but they are **dynamic structures** i.e. their numbers increase and decrease by the effect of various stimuli as well as according to the hormonal blood level. In the latter case, the regulation of the hormonal receptors is 2 types :

1. Up regulation : A low blood level of a certain hormone leads to an increase in the number of its active receptors.

2. Down regulation : A high blood level of a certain hormone leads to a decrease in the number of its active receptors. In case of cell membrane receptors, this occurs by either (a) **Endocytosis of the receptors** (= **internalization**) or (b) **Desensitization of the receptors** (i.e. the receptors are chemically modified in ways that make them less responsive).

MECHANISM OF ACTION OF HORMONES

Hormones are chemical messengers (= **ligands**) that carry signals (or messages) to the target cells to produce certain responses. The first event in

this process is *binding of the hormones to their specific receptors* in these cells. Such binding produces conformational changes in the receptors, which lead to their activation. This initiates a sequence of reactions in the cells that finally cause the required response. This process is called *signal transduction*.

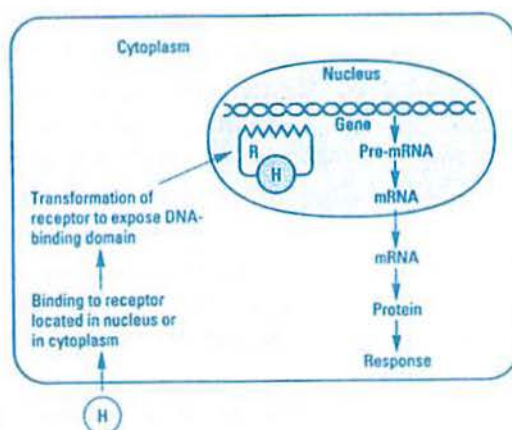


Figure 2 : Mechanism of action of steroid and thyroid hormones.

. R = Receptor , H = Hormone.

SIGNAL TRANSDUCTION PATHWAYS

Depending on the site of the hormonal receptors, signal transduction inside the target cells is produced by one of the following pathways :

(I) A pathway initiated by activation of the intracellular receptors

The hormones that act through this pathway are the fat-soluble hormones (= *lipophilic hormones*) that can cross the target cell membranes and enter inside these cells. These hormones include (a) The *steroid hormones*, which combine to receptors located in the *cytoplasm of the target cells* (b) The *thyroid hormones* (T_3 and T_4), which combine to receptors located in the *nuclei of the target cells*.

The activated receptors in both cases (i.e. the receptor-hormone complexes) bind to DNA in the nuclei of the target cells and this increases *transcription of specific mRNAs*. These pass to the cytoplasm where they are

translated in the ribosomes, leading to production of increased quantities of regulatory proteins that alter the cell functions and, consequently, lead to the required responses (figure 2).

HEAT SHOCK PROTEINS (HSP) OR STRESS PROTEINS

These are cytoplasmic proteins that increase when the cells are exposed to heat and other stresses, and they help the cells to survive in these conditions.

The receptors of the glucocorticoid hormones (= *steroid hormones secreted by the adrenal cortex and exert powerful antistress effects*) are bound to one of these proteins (**HSP 90**) and this protein covers the DNA binding sites in absence of the hormones. The secretion of these hormones increases in cases of stress, and when they bind to their receptors, the HSP 90 is released. This exposes the DNA binding sites, which initiates the required antistress responses (page 52). Other steroid hormone receptors e.g. *progesterone receptors* are also bound to heat shock proteins (page 132).

(II) Pathways initiated by activation of cell membrane receptors

The hormones that act through these pathways are the water-soluble hormones (= *hydrophilic hormones*) which include *all protein hormones except the thyroid hormones T_3 & T_4 which are lipophilic* (see above).

Activation of the receptors of these hormones can produce cell responses *by both direct and indirect pathways* (the later through activating certain proteins in the cell membranes called **G proteins**).

(A) The direct pathways that produce cell responses

1. *Activation or inactivation of ion channels* (i.e. opening or closing these channels respectively) e.g. Na^+ and K^+ channels. This affects the rates of influx and efflux of these ions, which consequently alter the cell functions and leads to the required responses.

2. *Increasing the activity of the tyrosine kinase enzyme* (which is present in the cytoplasmic portion of the receptor). This enzyme catalyzes *phosphorylation of certain cytoplasmic proteins*, which alters the cell functions and leads to the required response. The main hormone that acts by this mechanism is *insulin*.

3. *Stimulation of the Guanylyl (= guanylate or guanyl) cyclase enzyme which converts GTP (Guanosine-Tri-Phosphate) into c GTP (cyclic GTP).*

The latter acts as a **second messenger** that activates a specific **cGTP-dependent kinase enzyme**. This enzyme catalyzes **phosphorylation of certain cytoplasmic proteins**, which alter the cell functions and lead to the required response. The main hormone that acts by this mechanism is **ANP** i.e. the **atrial natriuretic peptide** (page 2).

THE G PROTEINS

The G proteins are regulatory proteins located in the cell membranes. They are **nucleotide-binding proteins that bind GTP** (so they are called GTP-binding proteins or simply G proteins) and they play an essential role in the translation of signals to biologic effects inside the cells (see below). They are 2 types ; **small and large**, and either may be stimulatory (**G_s proteins**) or inhibitory (**G_i proteins**). *Activation of the G_s proteins produces cell responses, while activation of the G_i proteins prevents these responses.* The large G proteins are made up of 3 subunits (**alpha, beta and gamma**) and are called **heterotrimeric G proteins** (figures 3 and 4).

THE SERPENTINE RECEPTORS

All the **heterotrimeric G protein-coupled receptors** are proteins that **span over the cell membrane and cross it 7 times like a snake** (figures 3 and 4), so they are called **serpentine receptors** (serpent = snake).

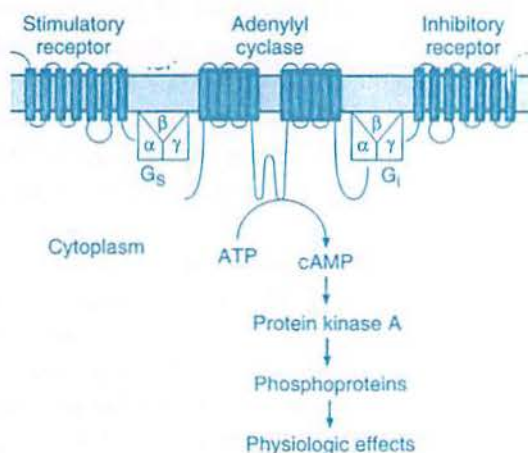


Figure 3 : Mechanism of action of hydrophilic hormones by formation of cAMP. Notice the structure of the serpentine receptors and adenylyl cyclase.

(B) The indirect pathways that produce cell responses (through activating G proteins)

Most hydrophilic hormones produce cell responses by this mechanism. In this case, the hormones act as *first messengers* that activate their receptors. The activated receptors then *activate the associated Gs proteins*, which induce formation of another intracellular chemical mediators (= *second messengers*) and these produce the required cell responses. The commonest indirect pathways and their associated second messengers include the following :

1. Cyclic AMP (cAMP) pathway

The activated Gs protein activates the *Adenylyl (= adenylyl or adenylate) cyclase enzyme* (a long polypeptide that crosses the cell membrane 12 times) which *catalyzes formation of cAMP from ATP* (figure 3). cAMP then activates a specific cAMP dependent kinase enzyme (= *protein kinase A*) which catalyzes *phosphorylation of a certain protein*. This alters its conformation (configuration) & function. Consequently the cell functions are changed, leading to the required response.

****** The hormones that act via increasing cyclic AMP include *ACTH, calcitonin, glucagon, parathormone, lipotropin, Human chorionic gonadotropin (hCG), MSH, TSH, Vasopressin (at the V_2 receptors), FSH and LH, most hypophysiotropic hormones (e.g. Gn-RH and TRH) and catecholamines (at all beta receptors).*

****** Some hormones act by *decreasing cyclic AMP* through stimulation of Gi proteins (figure 3). These include *somatostatin, catecholamines (at the α_2 receptors) and dopamine (at the $D_{2,3 \& 4}$ receptors).*

****** The activated Gs proteins can also stimulate the *phosphodiesterase enzyme (PDE)*. This enzyme catalyzes conversion of *cyclic GMP to 5'-GMP*, so *the intracellular content of cyclic GMP decreases* and this initiates the cell response. The main receptors that act by this mechanism are the *photoreceptors* (rods and cones) in the retina (refer to special senses).

2. Calcium - Calmodulin pathway

The activated Gs protein triggers opening of various ion channels in the cell membrane, particularly Ca^{2+} channels. Accordingly, the Ca^{2+} influx into the cells from the extracellular fluid increases. This Ca^{2+} *also stimulates Ca^{2+} release from the endoplasmic reticulum*, so the cytoplasmic Ca^{2+} content markedly increases. Ca^{2+} acts as a *second messenger* and combines with one of the Ca^{2+} - *binding proteins* particularly *calmodulin*.

The Ca^{2+} - *calmodulin complex* activates specific protein kinase enzymes which catalyze *phosphorylation of certain proteins*. This alters their conformation and functions. Consequently the cell functions are changed, leading to the required response. The *oxytocin* hormone increases the intracellular Ca^{2+} content probably by this mechanism.

3. Inositol triphosphate (IP_3) & Diacyl glycerol (DAG) pathway

Activation of Gs proteins activates the *phospholipase C enzyme* which catalyzes formation of both IP_3 and DAG by hydrolysis of *phosphatidylinositol diphosphate (PIP_2)*. IP_3 diffuses into the *endoplasmic reticulum* and causes release of Ca^{2+} into the cytoplasm (figure 4) which produces cell responses. On the other hand, DAG activates *protein kinase C* which alters the cell functions and produces the required responses (as protein kinase A in case of cyclic AMP).. Many hormones act by this mechanism including *norepinephrine (at the α_1 receptors)*, *angiotensin II* (increases DAG), *Vasopressin (at the V_1 receptors)* and *probably also oxytocin* (the latter 2 act by increasing formation of IP_3).

4. Arachidonic acid pathway : Activation of Gs proteins leads to activation of the *phospholipase A_2 enzyme*, which catalyzes conversion of certain phospholipids in the cell membrane into *arachidonic acid*. This acid acts as a second messenger that leads to formation of many substances e.g. prostaglandins, thromboxanes and leukotrienes, which alter the cell functions and produce the required responses.

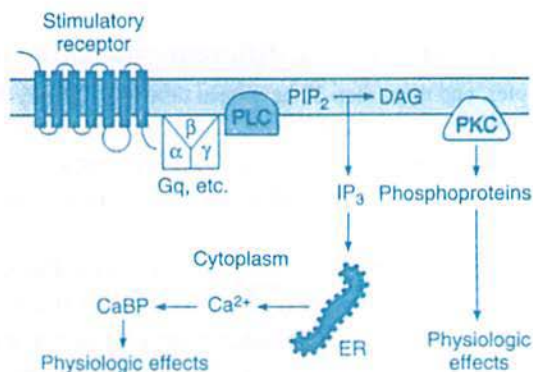


Figure 4 : Mechanism of action of hydrophilic hormones by formation of DAG and IP_3 . PLC = Phospholipase C, PKC = Protein kinase C, ER = Endoplasmic reticulum, CaBP = Calcium binding protein.

CHAPTER 2

THE PITUITARY GLAND (THE HYPOPHYSIS)

This is a small gland, 0.5-1 gm in weight, situated at the base of the skull in a small cavity called the *sella turcica* (= *hypophysial fossa*), and is attached to the floor of the 3rd ventricle of the brain by a stalk (= *pituitary stalk or infundibulum*). It consists of 3 lobes (figure 5b) : A large anterior lobe called the *adenohypophysis or anterior pituitary gland*, a small *intermediate lobe* (which is rudimentary in humans) , and a large posterior lobe called the *neurohypophysis or posterior pituitary gland*.

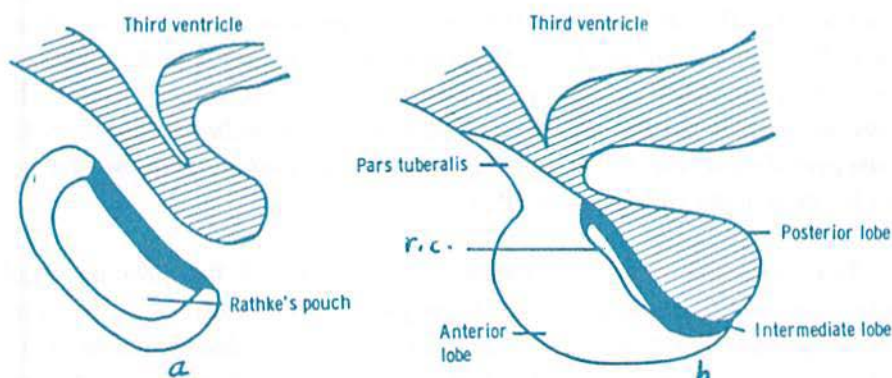


Figure 5 : Development of the pituitary gland (a) and its lobes (b).
r.c. = residual cleft.

The gland develops from 2 different structures (figure 5a) : An *upward ectodermal growth* from the roof of the pharynx known as the **Rathke's pouch**, and a *downward neural growth* from the floor of the 3rd ventricle of the brain. These meet in the sella turcica, and the stalk of the Rathke's pouch degenerates while that of the neural growth persists and forms the *pituitary stalk*.

The Rathke's pouch develops into 3 parts (1) **Pars distalis** (= pars glandularis) which develops from the anterior wall of the Rathke's pouch (2) **Pars tuberalis** which is an upward extension of the pars distalis (3) **Pars intermedia** which develops from the dorsal half of the Rathke's pouch. Both the pars distalis and the pars tuberalis form the anterior lobe of the gland while the pars intermedia forms the intermediate lobe. The downward neural

growth develops into the **pars nervosa** (forming the posterior lobe) to which the intermediate lobe becomes closely adherent and is separated from the anterior lobe by the remains of the Rathke's pouch known as the residual cleft (figure 5 b).

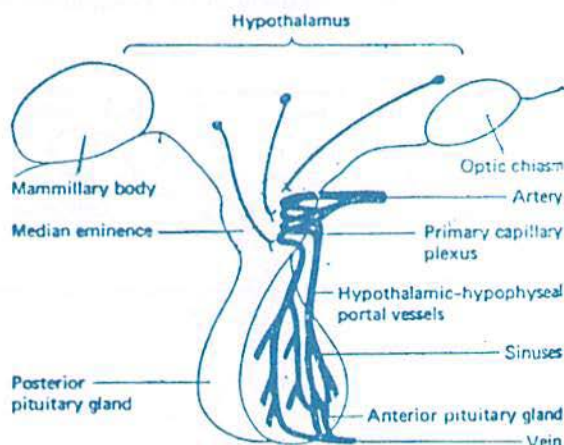


Figure 6 : The hypothalamo-hypophyseal portal circulation.

HYPOTHALAMIC CONNECTIONS WITH THE PITUITARY GLAND

There are 2 types of connections between the hypothalamus and the pituitary gland (which form a link between the nervous system and the gland) :

1- A *vascular connection between the hypothalamus and anterior lobe* in the form of a **hypothalamo-hypophyseal portal circulation** (figure 6). Arterial twigs from the carotid arteries form a *primary capillary plexus* in the basal part of the hypothalamus known as the *median eminence* from which blood is drained by *portal hypophyseal vessels* down in the pituitary stalk to a *secondary capillary plexus in the anterior lobe* (which then drains into the hypophyseal vein)

2- A *nervous connection between the hypothalamus and posterior lobe* in the form of a **hypothalamo-hypophyseal tract** (figure 7).

THROUGH THESE CONNECTIONS THE HYPOTHALAMUS ACTS AS A CONTROL CENTRE TO THE ENDOCRINE SYSTEM AS FOLLOWS :

(1) The hypothalamus secretes several hormones called *hypophysiotropic hormones* (see below) from an area called the *hypophysiotropic area* (which includes the preoptic, arcuate and ventromedial nuclei). These hormones are

Section 1- Chapter 2

The pituitary gland (the hypophysis)

then *released from the median eminence into the portal vessels* through which they reach the anterior pituitary gland where they affect the secretion of its hormones. In this way, *the hypothalamus indirectly controls the activity of most of the endocrine system* because the anterior pituitary gland secretes tropic hormones that control most of the other endocrine glands (see below).

(2) The hypothalamus also *secretes the 2 hormones of the posterior pituitary gland*, which are transported via the hypothalamo-hypophyseal tract

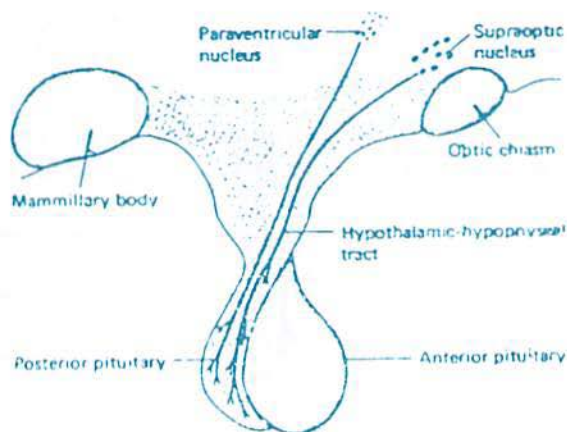


Figure 7 : The hypothalamo-hypophyseal tract.

by axonal flow to the posterior pituitary gland where they are stored then released when required by signals discharged from the hypothalamus (see the posterior pituitary gland, page 27).

****** The hypothalamus is connected to almost all areas in the nervous system. This explains why endocrinal disturbances frequently occur secondary to emotions, psychological disorders and other nervous diseases.

****** The hypothalamus contains *osmoreceptors, thermoreceptors and glucoreceptors* which detect the plasma osmolality, body temperature and blood glucose level respectively. It then corrects any detected disturbance by changing the rate of secretion of its hormones according to the underlying condition (refer to metabolism and kidney).

THE ANTERIOR PITUITARY GLAND (ADENOHYPHYSIS)

This gland secretes 7 *protein hormones*, which are classified as follows :

(1) Polypeptide hormones : These include the following :

1. *Adrenocorticotrophic hormone* (= ACTH or corticotropin).
2. *Prolactin* (= PRL, Mammatropin or Lactogenic hormone, LGH).

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The pituitary gland (the hypophysis)

3. **Growth hormone** (= Somatotrophic hormone, STH or Somatotropin).
4. **Beta lipotropin** (B-LPH), a polypeptide that contains the amino acid sequences of *endorphins* and *enkephalins*.

(2) Glycoprotein hormones : These include the following hormones :

1. **Thyroid stimulating hormone** (TSH, thyrotropic hormone, thyrotropin).
2. **Luteinizing hormone** (= LH) or **interstitial-cell stimulating hormone**.
3. **Follicle stimulating hormone** (= FSH).

****** Both FSH and LH control the gonads in the males and females, so they are called together the **gonadotropic hormones** (= GTHs).

****** The anterior pituitary gland is frequently called the **master gland** because it secretes tropic hormones that control most of the other endocrine glands (ACTH controls the adrenal cortex, TSH controls the thyroid gland, while the GTHs control both male and female gonads).

****** **Tropic hormones stimulate secretion from other endocrine glands except somatotropin (the growth hormone)** because the latter is a systemic hormone that is not tropic to any specific endocrine gland.

CELL TYPES IN THE ADENOHYPOPHYSIS

The cells of the **anterior lobe of the anterior pituitary gland** are traditionally classified on the basis of their staining reactions into **2 types** :

(1) Chromophobe cells :

These cells do not stain with either acidic or basic dyes and they are *inactive secretory cells that contain few secretory granules*.

(2) Chromophil cells :

These are *granular secretory cells* and they are 2 types :

1. **Acidophilic cells** : These stain with acidic dyes and they are 2 types :

- a- **Somatotropes** which secrete somatotropin (GH).
- b- **Mammotropes (or lactotropes)** which secrete prolactin.

2. **Basophilic cells** : These stain with basic dyes and they are 3 types :

- a- **Thyrotropes** which secrete TSH.
- b- **Gonadotropes** which secrete the GTHs (LH and FSH).
- c- **Corticotropes** which secrete ACTH, beta Lipotropin (B-LPH) as well as the opioid peptide **beta endorphin**.

****** The anterior pituitary gland also contains **folliculostellate cells** which secrete the **cytokine interleukin 6** (but their physiological role is unknown).

THE INTERMEDIATE LOBE

This contains basophilic cells that synthesize a large precursor protein called *pro-opiomelanocortin (POMC)*. This is hydrolyzed to *gamma lipotropin* (unknown functions), *B-endorphin* as well as *alpha & beta melanocyte-stimulating hormones* (= *MSHs, melanotropin or intermedin*). The MSHs accelerate melanin synthesis by the melanocytes, and treatment with these hormones in humans produces detectable skin darkening in 24 hours. However, the **intermediate lobe is rudimentary in humans**, and it appears that *both alpha and beta-MSHs are not secreted in adult humans*.

****** The corticotropes also synthesize *pro-opiomelanocortin (POMC)* but it is hydrolyzed into *ACTH, beta lipotropin and a small amount of B-endorphin*.

****** The MSHs and ACTH are structurally inter-related because both are derived from POMC. This, together with absence of MSHs in humans and presence of *melanotropin receptors in the melanocytes that can bind ACTH* led to the fact that the *pigmentary changes in several endocrine diseases are due primarily to changes in the blood level of ACTH (which exerts a considerable MSH activity)* e.g. the abnormal pigmentation that occurs in Addison's disease is due to increased ACTH secretion (page 60) while the pallor observed in panhypopituitarism is due to deficient ACTH secretion (page 26).

REGULATION (CONTROL) OF ANTERIOR PITUITARY SECRETION

The secretion of the anterior pituitary hormones is controlled by the *hypothalamus as well as by feedback mechanisms*.

(A) HYPOTHALAMIC CONTROL

The hypothalamus controls the activity of the anterior pituitary gland by releasing hormones called *the hypophysiotropic hormones* that reach the gland via the *hypothalamo-hypophyseal portal circulation*. These hypothalamic hormones are *polypeptides* that act mostly by increasing the intracellular content of *cyclic AMP* and they either *stimulate release of the anterior pituitary hormones* (= **releasing hormones**) or *inhibit the release of these hormones* (= **release-inhibiting hormones**).

Because of the numerous inter-connections between the hypothalamus and other areas of the nervous system, the latter influences most of the endocrine system through the *neuroendocrine regulation of the anterior pituitary gland by the hypophysiotropic hormones*.

Hypothalamic hormones (hypophysiotropic hormones)

(1) Releasing hormones :

1. *Corticotropin-releasing hormone* or CRH (stimulates ACTH secretion).
2. *Thyrotropin-releasing hormone* or TRH (stimulates TSH secretion).
3. *Growth hormone-releasing hormone* (GRH).
4. *Gonadotropin-releasing hormone* (GnRH).
5. *Prolactin-releasing hormone* or PRH (stimulates prolactin secretion).

(2) Release-inhibiting (or inhibiting) hormones :

1. *Growth hormone-inhibiting hormone* (GIH or somatostatin).
2. *Prolactin-inhibiting hormone* (PIH, which was chemically found to be dopamine). It exerts a tonic inhibitory effect on the mammotropes.

****** The activity of the anterior pituitary gland is largely controlled by the hypophysiotropic hormones. All anterior pituitary hormones are controlled mainly by their releasing hormones **except prolactin** which is controlled mainly by PIH (see above). This explains why section of the pituitary stalk decreases secretion of all anterior pituitary hormones except the secretion of prolactin which temporarily increases (page 147).

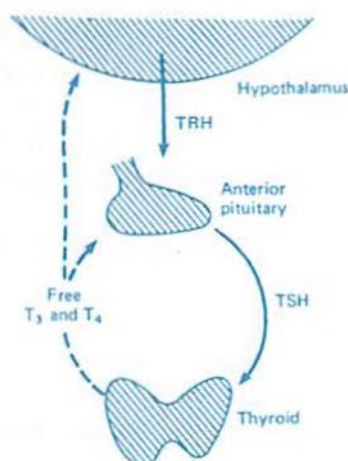


Figure 8 : Negative feedback mechanisms that control secretion of the thyroid hormones. Dashed arrows indicate inhibition.

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The pituitary gland (the hypophysis)

(B) FEEDBACK MECHANISMS

These constitute the relations between the blood levels of the hormones and the secretory rate of their pituitary tropic hormones as well as the hypothalamic hypophysiotropic hormones. Such relations are 2 types :

1. Positive feedback : This mechanism acts only in *certain situations*. If the blood level of a certain hormone is increased, it stimulates the secretion of its corresponding pituitary tropic hormone or hypothalamic releasing hormone, leading to *a further increase in its blood level*.

2. Negative feedback : This mechanism *is more common*. If the blood level of a certain hormone is increased, it will be rapidly reduced to its normal level, and vice versa. It is produced by a direct effect of the hormonal blood level on the secretory rate of either the pituitary tropic hormones, the hypophysiotropic hormones or both together e.g. if the blood levels of the thyroid hormones increase, they will be reduced to their normal levels through inhibiting the secretion of both TSH and TRH (figure 8).

THE GROWTH HORMONE (GH)

The human anterior pituitary gland secretes **2 biologically active types of GHs**, the first (about 75 %) is a protein hormone consisting of 191 amino acids and has a molecular weight 22000, while the other is smaller than the first (it lacks 15 amino acids and has a molecular weight 20000). They *structurally resemble prolactin and the placental growth hormones* (page 138). In normal adults, its daily output is 0.2-1 mg and its basal plasma level is 2-4 ng/ml (and 5-8 ng/ml in children). *The monkey's GH is the only GH from animals that can safely be given to humans.*

EFFECTS (ACTIONS) OF THE GROWTH HORMONE (GH)

A. INDUCTION OF GROWTH

Growth involves *an increase in the body mass*, and the GH is *the principal growth promoting factor* in the body. It induces growth through increasing the rates of both protein synthesis and cell division as well as by exerting *many metabolic effects* (see below) that lead to *retention of all elements required for growth* (including amino acids, calcium, phosphates and other electrolytes). The GH causes the following :

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1- Growth of almost all soft tissues in the body including *skeletal muscles, skin and most viscera*. However, it does not affect the nervous tissues and does not produce tissue maturation (which is mainly a function of the thyroid hormones) and it also **increases the metabolic rate**.

2- **Chondrogenesis** (= cartilage formation) which is followed by ossification and growth of bones. In long bones, if the epiphyses are not yet fused to the bones (the case in children), as the cartilaginous epiphysal plates widen (figure 9), they lay down more bone matrix at the ends of these bones, so their lengths increase leading to increase in the body stature.



Figure 9 : Effect of GH on growth of the epiphysal plate. Before giving the hormone (left) and after giving the hormone (right).

B. METABOLIC EFFECTS

1. **Protein metabolism :** The GH is a *protein anabolic hormone*. It increases the uptake of amino acids and protein synthesis in the tissue cells. Therefore, it produces a *positive nitrogen balance* together with a decrease in the blood levels of urea and amino acids.

2. **Electrolyte metabolism :** The GH increases the gastrointestinal absorption of Ca^{2+} and also produces a *positive phosphorus balance*. It also *decreases the rate of urinary excretion of both Na^{+} and K^{+}* (so these electrolytes are diverted to the growing tissues).

3. **Fat metabolism :** The GH mobilizes fat from adipose tissues and *stimulates lipolysis*, so it decreases the body fat content and increases the blood level of the *free fatty acids (FFAs) and ketone bodies*. The FFAs provide a ready source of energy for the tissues, which spares proteins (thus promoting protein synthesis). This *protein sparing effect of the GH* maintains its growth effect in hypoglycemia, fasting and stress, and is the main function of the hormone in adults (in whom the growth hormonal blood level is low but important, not for growth but for maintenance of the tissue mass by its protein sparing effect).

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4. Carbohydrate metabolism : The growth hormone is *diabetogenic* (i.e. it increases the blood glucose level) by (a) *Increasing the hepatic glucose output* (b) Exerting *an anti-insulin effect* (decreasing glucose uptake by the tissues specially skeletal muscles) through reducing the ability of the tissues to bind insulin and also because FFAs are readily available.

The GH also *increases the sensitivity of the pancreatic insulin-secreting cells (the B cells) and their response to various stimuli (specially insulinogenic stimuli e.g. glucose and arginine)*. For this reason, *administration of GH may initially cause temporary hypoglycemia* but it will eventually increase the blood glucose level. The resulting hyperglycemia *facilitates the release of insulin, which is an additional way to promote growth* (since insulin also exerts an anabolic effect). However, prolonged secretion (or administration) of the GH leads to *exhaustion of the B cells*, and accordingly insulin secretion will be decreased resulting in frank diabetes called *pituitary (or hypophyseal) diabetes*.

SOMATOMEDINS

These are *polypeptide growth factors* that are secreted *by the liver* as well as by *cartilage and other organs*. There are a variety of different somatomedins, the principal of which in man are *insulin-like growth factor I (= IGF-I or somatomedin C) and IGF-II*. The *secretion of IGF-I is stimulated by the GH only after birth*. On the other hand, the secretion of *IGF-II is largely independent of the GH and it plays a role in fetal growth before birth* (however, the stimuli that cause its release are unknown, and in adults, it is synthesized only in the *choroid plexus and meninges*). The structure of these factors is *closely related to insulin* (hence the name) and they exert the following actions :

1. They have a *weak insulin-like activity*.
2. They induce *protein synthesis, growth and chondrogenesis*.
3. They *inhibit lipolysis*.

****** The *GH does not produce most of its effects by itself, but through IGF-I*, the presence of which is essential e.g. protein synthesis and chondrogenesis are *presumably produced only by IGF-I*. However, it was suggested that *GH combines with IGF-I in various proportions to produce its effects* and in case of chondrogenesis, it is believed that the GH acts on cartilage to convert its stem cells into cells that respond to IGF-I, then the locally-produced and circulating IGF-I make the cartilage grow.

****** In addition to its growth & metabolic actions, the GH also exerts *an intrinsic lactogenic activity* due to its *structural resemblance to prolactin*.

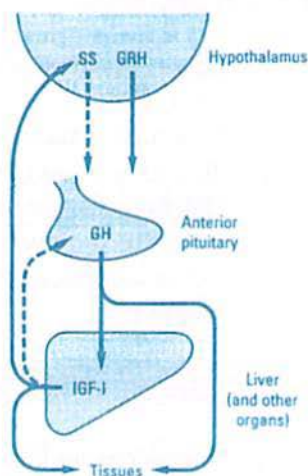


Figure 10 : Feedback control of secretion of the growth hormone. Dashed arrows indicate inhibition.

CONTROL OF GROWTH HORMONE SECRETION

The secretion of GH is controlled by (a) *Feedback mechanisms* (b) 2 hypophysiotropic hormones, **GRH** and **GIH** (= *somatostatin*) (c) A newly discovered 28 amino acid polypeptide called **Ghrelin** : This is secreted from the stomach and hypothalamus, and it exerts a marked GH-stimulating activity. The rate of GH secretion undergoes marked fluctuations in response to a variety of stimuli (specially in children and young adults before it declines in old age) as follows :

(A) Stimuli that increase GH secretion

1. Deficiency of the energy-producing substrates (e.g. in hypoglycemia and fasting) or increased demand to them (e.g. during exercise).
2. Increased blood levels of certain amino acids (e.g. arginine), so a rich-protein meal stimulates GH secretion.
3. Stressful stimuli e.g. psychologic stresses.
4. Going to sleep (at the beginning of normal non-REM sleep).
5. Certain drugs and hormones e.g. glucagon, noradrenaline, estrogens, androgens, 2-deoxyglucose, alpha-receptor adrenergic stimulating drugs, L-dopa and dopamine-receptor agonists (e.g. apomorphine).

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1. Increased blood glucose level (i.e. hyperglycemia).
2. During REM sleep (refer to C.N.S.).
3. Increased blood levels of certain hormones e.g. cortisol.
4. Increased blood level of free fatty acids (FFAs), possibly by inhibiting release of the GH from the anterior pituitary gland by a *negative feedback mechanism* (see below).
5. When the IGF-I blood level is increased (*by a negative feedback mechanism* as described below).

FEEDBACK CONTROL OF GH SECRETION

The hypothalamic growth hormone-releasing hormone (GRH) stimulates GH secretion from the anterior pituitary gland. GH stimulates release of IGF 1 from many organs *particularly the liver* (figure 10) and IGF 1 in turn inhibits the release of GH by **(a)** a direct action on the anterior pituitary gland and **(b)** stimulating the release of somatostatin (SS) from the hypothalamus.

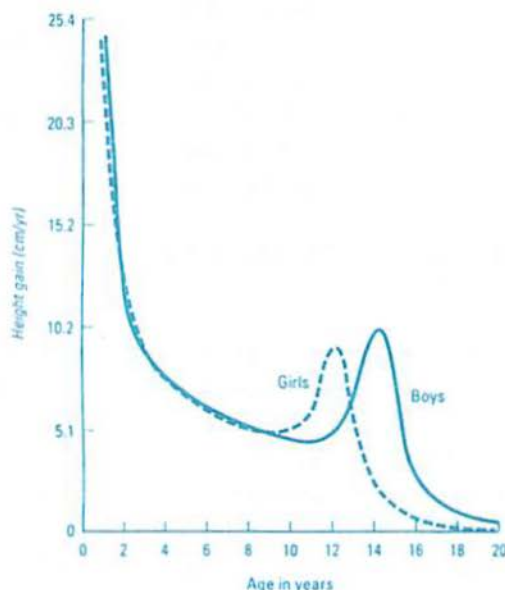


Figure 11 : The rate of growth in boys and girls from birth to 20 years of age.

PHYSIOLOGY OF GROWTH

RATE OF GROWTH

Fetal growth is independent of the fetal GH, and it depends only on fetal IGF II (page 18). After birth, growth normally continues till the age of about 20 years in males and 18 years in females. The growth rate is high in the first year then it declines at first rapidly then slowly till puberty at which there is a spurt of growth (after which it declines till it stops due to fusion of the epiphyses to the bones). Therefore, there are **2 periods of rapid growth** the first **in infancy** and the second in **late puberty** (figure 11). Infantile growth after birth is partly a continuation of fetal growth (depending on IGF II) but the GH and thyroid hormones soon contribute, and it is **episodic** (i.e. there are short periods of accelerated growth that are separated by long periods of non-detectable growth). On the other hand, pubertal growth is produced by the combined effects of the GH and **sex hormones**.

FACTORS THAT CONTROL GROWTH

(A) **Genetic factors** : These determine the rate and limit of growth.

(B) **Extrinsic factors** : These include the following :

1. **Nutrition (food supply)** : This is the most important extrinsic factor that affects growth. Diet should contain adequate amounts of proteins, vitamins and minerals as well as calories (in the form of carbohydrates and fats), so that the proteins are used only to promote growth.
2. **Disease or injury** : These delay growth because they increase protein catabolism. However, for unknown reasons, following a period of illness or starvation in children, there is a period of accelerated rate of growth (= **catch up growth**) that continues until the normal rate is reached
3. **Stress and emotions** : Certain stressful and emotional conditions may be associated with retarded growth (*see in the causes of dwarfism and short stature, page 23*).

(C) **Hormones** : Growth is affected not only by the GH but also by :

1. **Thyroid hormones** : These hormones are **essential for normal growth**. They contribute with the GH and somatomedins in *promotion of growth in the early few months after birth*, and after that their action is **permissive to that of the GH** (possibly by potentiation of

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the actions of somatomedins).i.e. the GH exerts its actions only in presence of these hormones. They also stimulate GH secretion and are essential for *tissue maturation* and *brain development*. They also have marked effects on ossification of cartilage, teeth growth, the contours of the face and the proportions of the body, so hypothyroid infants (who are called *cretins*) are dwarfed, mentally retarded, and have infantile features (page 44).

2. Glucocorticoid hormones : At normal secretory rates, these hormones exert a permissive action on growth by maintaining constant the various body conditions specially the circulation and blood pressure. However, excess glucocorticoids inhibit growth because of their *direct catabolic action on the cells* (page 51).

3. Insulin : Diabetic animals fail to grow due to lack of the anabolic action of insulin, and insulin causes growth in hypophysectomized animals but only when great amounts of carbohydrate and protein are supplied with insulin (page 87).

4. Sex hormones : These hormones cause a spurt of growth at puberty by (a) *Interaction with the GH and IGF I* (they stimulate secretion of GH which increases IGF I that causes growth) (b) Producing a marked *anabolic effect*, particularly androgens (= male sex hormones), the secretion of which *increases in both sexes at puberty*. In males, androgens are secreted from both the testes and the adrenal cortex, while in females they are secreted from the adrenal cortex only. The female sex hormones (= estrogens) exert similar (but weaker) effects as those of androgens.

Sex hormones initially stimulate growth, but they rapidly terminate it, *specially estrogens* (i.e. *their action on growth is self-limiting*) by causing fusion of the epiphyses to the long bones (so linear growth will stop). This *explains why* (a) Pituitary dwarfs (see below) treated with androgens grow first a few inches then stop (b) Eunuchs (castrated male individuals before puberty) tend to be tall (due to deficiency of the sex hormones) (c) Patients with sexual precocity (early puberty) are liable to be dwarfs (due to the action of the sex hormones, which cause early fusion of the epiphyses to the long bones).

CAUSES OF DWARFISM (short stature or stunted growth)

1. Deficient GH secretion : This may be due to either a pituitary disease or deficient secretion of GRH from the hypothalamus. Isolated GH deficiency leads to *dwarfism*, while its deficiency together with the GTHs leads to *infantilism* (see below).

2. Cretinism (= hypothyroidism in infants) (page 44).

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3. **Laron dwarfism (= growth hormone insensitivity)** : This is a condition of stunted growth *although the plasma GH level is normal or even elevated*. It occurs as a result of unresponsiveness of the GH receptors to the growth hormone, which leads to *deficiency of the circulating somatomedins* (resulting in stunted growth).

4. **Precocious puberty** (see above).

5. **Certain bone and metabolic diseases**.

6. **Genetic causes e.g. the dwarfism that occurs in achondroplasia and African pygmies** (= a dwarf race in equatorial africa).

7. **Some chromosomal diseases e.g. Turner's syndrome** (page 100).

8. **Constitutional delayed growth** (short stature with unknown causes).

9. **Chronic abuse and neglect in children (= Psychosocial dwarfism that is known as the Kaspar Hauser syndrome)**.

**** Pituitary dwarfism is better than both infantilism and cretinism because the patient is only short.** In the latter 2 conditions, the patient is short and also has hypogonadism. In cretinism, there is, in addition, mental retardation.

**** Treatment of any type of dwarfism should begin before puberty.**

DISEASES OF THE ANTERIOR PITUITARY GLAND

(A) Excessive secretion of GH

This results from *an acidophil somatotrope cell tumour* which secretes large amounts of GH. It causes **Gigantism** in children and **Acromegaly** in adults.

(1) Gigantism (= giantism)

This disease is due to excessive secretion of the GH *in children i.e. before union of the epiphyses*. It is characterized by the following :

1. Overgrowth of the skeleton in **normal proportions**, so the stature increases to **2 meters or more** (7-8 feet) and osteoarthritis may occur.
2. Overgrowth of soft tissues and viscera (= **splanchnomegaly**).
3. **Infantile gonads** may be present due to pressure of the tumour on the gonadotropes (which leads to decreased secretion of the GTHs).
4. **Diabetes mellitus** may develop due to the diabetogenic effect of GH.
5. Signs due to **local effects of the tumour** may appear (see below).

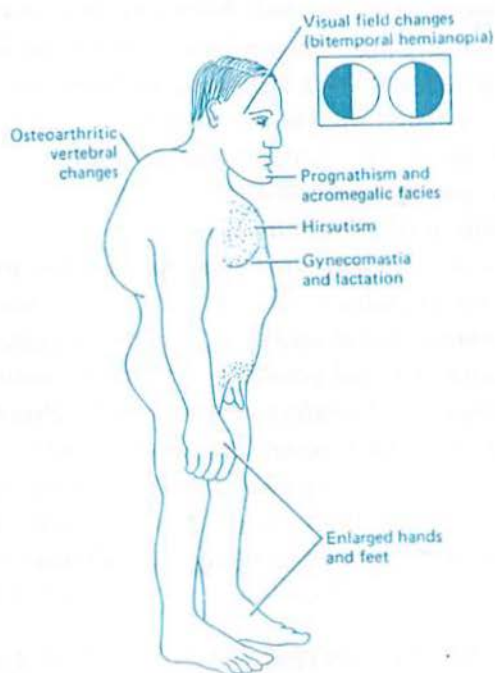


Figure 12 : Typical findings in acromegaly.

(2) Acromegaly

This disease is due to excessive secretion of the GH *in adults i.e. after union of the epiphyses*. It is characterized by the following (figure 12) :

1. **Thick bones**, but there is **no linear growth**. The acral parts (specially the hands and feet) are markedly enlarged (hence the name).

2. Enlargement of the lower jaw (the mandible) leading to forward protrusion of the chin (= **prognathism**). This together with overgrowth of the facial bones and enlargement of the supraorbital ridges, lips, ears and nose produce coarse facial features called the **acromegalic faces**.

3. Overgrowth of the **vertebrae** leading to **kyphosis** (which commonly predisposes to **osteoarthritis**).

4. Overgrowth of viscera (= **splanchnomegaly**) and other soft tissues. The skin becomes coarse and thick, and that of the forehead and scalp is thrown into wrinkles (= **bulldog scalp**). The enlargement of the heart may predispose to **myocardial ischemia and cardiomyopathy**.

5. The body and limb hair is increased (= **hirsutism**) and the male sex organs may enlarge because the GH increases the actions of androgens.

6. In 25 % of patients, there are **signs of diabetes** due to the **diabetogenic effect of the GH**.

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7. **Gynecomastia** (= enlargement of breasts in males) and **lactation in 4 % of non-pregnant female patients** (due to the lactogenic effect of GH).

8. Signs due to **local effects of the pituitary tumour**. These include :

(a) *Enlargement of the sella turcica.*

(b) Changes in the visual fields in the form of *bitemporal hemianopia*, due to pressure of the pituitary tumour on the *central part of the optic chiasma* (refer to special senses).

(c) *Headache, blurring of vision and vomiting* (due to increase of the intracranial pressure).

**** Hypersecretion of the GH by a pituitary somatotrope tumour can be treated by either** (1) Surgical removal of the tumour (2) Destruction of the tumour by irradiation (3) Drugs or hormones that inhibit the release of the GH (e.g. somatostatin).

**** Signs of adrenocortical hyperfunction** (known as **Cushing disease**) can be produced as a result of excess ACTH secretion by *ACTH-secreting pituitary tumours*. Such tumours (and the ACTH-secreting tumours that can develop in other tissues) are often difficult to detect (page 61).

(B) Deficient secretion of GH

GH deficiency in young individuals before puberty causes **dwarfism (or infantilism)** if accompanied by failure of sexual development due to simultaneous deficiency of the GTHs). **In adults, GH deficiency causes decrease of the tissue mass** (page 17). **Pituitary dwarfism** is characterized by :

1. Arrested skeletal growth (the patient's height is 100-120 cm in adult life). Temporary little growth occurs at puberty (by androgens).
2. The stunted skeletal growth is **symmetrical**, so the body proportions are like child's (but the head tends to be large relative to the body).
3. There is **acceleration of the aging process** (because the GH hormone exerts an **anti-aging action**).
4. The mental development is normal, and the patients are usually intelligent but emotionally unstable.
5. There is normal sexual maturity (since there is only GH deficiency).

(C) Panhypopituitarism (Simmond's disease)

This is *generalized failure of the anterior pituitary gland due to either damage by disease or necrosis in some women who have an episode of shock following severe postpartum hemorrhage (Sheehan's syndrome)*. It is characterized by the following manifestations :

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1- Arrested growth in children and acceleration of aging in adults producing premature senility (= *progeria*).

2- Atrophy of (a) The thyroid gland (leading to cretinism in children and myxedema in adults) (b) Some zones of the adrenal cortex (leading to inability to resist stress conditions) (c) The gonads, leading to *hypogonadism* which is manifested by impairment of sex functions in males (page 114) and stoppage of the sex cycles in females (page 135).

3- *Hypoglycemia* due to increased sensitivity to insulin caused by deficiency of the main insulin antagonists (i.e. the GH and glucocorticoids).

4- Severe pallor, mainly due to *lack of ACTH* (page 14).

5- Mild loss of weight due to lack of the anabolic effects of the GH and the androgens. However, cachexia or emaciation (severe loss of weight) may occur if there is *anorexia nervosa* (= *severe loss of appetite*).

****** Damage of the posterior lobe leads to severe diuresis due to lack of ADH (see posterior pituitary gland). However, *damage of both lobes of the pituitary gland leads only to mild diuresis*. This is due to reduction of the osmotic load delivered to the renal tubules that is caused by decreased secretion of both the glucocorticoids (which decreases protein catabolism) as well as the thyroid hormones (which decreases the metabolic rate).

FROHLICH'S SYNDROME

This disease is also known as the *adiposo-genital syndrome or hypothalamic eunuchism*. It occurs in children as a result of damage of certain hypothalamic areas, and is characterized by (a) *Infantile genital organs* due to decreased secretion of the GnRH (which reduces GTHs secretion from the adenohypophysis) (b) *Overeating and obesity* due to *disturbance of the appostat centre in the hypothalamus* i.e. the feeding and satiety centres (refer to metabolism).

THE POSTERIOR PITUITARY GLAND (NEUROHYPOPHYSIS)

This gland is made up of the following structures :

1. *Pituicytes* : These are modified astrocytes (= supporting neuroglial cells).
2. *Non-medullated nerve fibres* : These originate at the supraoptic and paraventricular nuclei of the hypothalamus and reach the gland in the pituitary stalk via the *hypothalamo-hypophyseal tract* (figure 7).
3. *Herring bodies* : These are granules of stored hormones.

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2 hormones are released (*not secreted*) from the gland. These are the **antidiuretic hormone** (= **ADH** or **vasopressin**) and **oxytocin**. Both hormones are *polypeptides* (each containing 9 amino acids) which are structurally similar except for 2 amino acids (in ADH, phenylalanine and arginine replace leucine and isoleucine in the oxytocin molecule). Since ADH contains arginine, it was also called **arginine vasopressin** (in some animals, arginine is replaced by lysine forming *lysine vasopressin*).

The 2 hormones are synthesized in the cell bodies of the **magnocellular neurons in both the supraoptic and paraventricular nuclei of the hypothalamus**, but ADH mainly (more than 80 %) in the supraoptic nucleus while oxytocin mainly (also more than 80 %) in the paraventricular nucleus). The hormones are then transported by **axoplasmic flow** down the axons of the magnocellular neurons to their endings in the posterior pituitary gland where they are stored as *Herring bodies* (till they are released in response to electrical activity in their endings). For this reason, these hormones are **typical neural hormones** (i.e. hormones secreted into the circulation by nerve cells).

Both hormones are synthesized from large precursor molecules called **neurophysins** (neurophysin I or **oxyphysin** in case of oxytocin, and neurophysin II or **pressophysin** in case of ADH). Cleavage of these precursor molecules occurs *during their down transport in the hypothalamo-hypophysial tract*, and the storage granules contain both the free hormones as well as their corresponding neurophysins.

MECHANISM OF RELEASE OF THE HORMONES

Stimulation of the hypothalamic nuclei initiates *action potentials* in their neurons which, on reaching the nerve endings, cause release of the hormones (*by Ca^{2+} dependent exocytosis*) together with their neurophysins, and all are absorbed into the local blood vessels, from which they reach the general circulation. The functions of the hormones are well known, but however, the functions of the neurophysins are unknown.

THE ANTIDIURETIC HORMONE (ADH OR VASOPRESSIN)

Functions (effects or actions) of ADH

(A) Water retention (an anti-diuretic effect) : ADH increases the permeability of the distal segments of the renal tubules, mainly the collecting ducts, thus promoting water reabsorption which results in water retention in the body and production of concentrated urine.

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Mechanism : ADH binds to special receptors in the tubular cells called V_2 **receptors**. Such binding leads to activation of the *adenylate cyclase enzyme* and increased formation of *cyclic AMP*, which causes *insertion of protein water channels called aquaporins in the luminal borders of the tubular cells*. This *increases the permeability of these cells to water*, and consequently *augments water reabsorption by passive diffusion under influence of the hyperosmolality of the renal medullary interstitium* that is produced by the countercurrent function of the loops of Henle (see kidney).

(B) Generalized vasoconstriction (V.C.) : In large doses only, ADH causes direct strong V.C. all over the body, which increases the arterial blood pressure (so the hormone is also called **vasopressin**).

Mechanism : ADH binds to special receptors in the arterioles called V_{1A} **receptors** which increase the cytoplasmic Ca^{2+} (through formation of *inositol triphosphate*, page 9) leading to smooth muscle contraction and V.C..

**** V_{1A} receptors** are also found in the *liver & brain* where ADH stimulates glycogenolysis in the former and acts as a neurotransmitter in the later.

**** There are another type of V_1 receptors called V_{1B} (or V_3) receptors** that are located in the *adenohypophysis*, where they *stimulate ACTH secretion*.

Factors that control the release of ADH

1. Plasma osmolality : Significant changes in ADH release occur when the plasma osmolality is altered by as little as 1 %, aiming at maintaining it *close to 285 mOsm/litre*. These changes are mediated through affecting certain *osmoreceptors located in the anterior hypothalamus* (these are located in the *organum vasculosum of the lamina terminalis* and are outside the blood brain barrier). Rise of the plasma osmotic pressure (e.g. due to dehydration) stimulates the osmoreceptors, which discharge signals that stimulate the ADH-secreting neurons in the hypothalamus. These neurons discharge impulses, which on reaching their terminals in the neurohypophysis stimulate the release of ADH. This causes water retention which decreases the plasma osmotic pressure back to its normal level. Opposite effects occur if the plasma osmotic pressure falls (e.g. due to overhydration).

2. Extracellular fluid volume : Changes in the ECF volume also affect ADH secretion. This is mediated through affecting *certain receptors*

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in the low and high-pressure portions of the vascular system.

The low pressure receptors are located in the *atria, great veins and pulmonary vessels*, while the high pressure receptors are those in the carotid sinus and aortic arch (*i.e. the arterial baroreceptors*).

The low pressure receptors monitor the fullness of the vascular system and are the primary mediators that effect release of ADH. A moderate decrease in the ECF volume (*i.e. hypovolemia*) stimulates these receptors, which discharge signals that stimulate the *hypothalamic ADH-secreting neurons* leading to ADH release from the neurohypophysis. This causes water retention, which increases the ECF volume back to its normal level. Hypovolemia also leads to secretion of renin from the kidneys and this leads to formation of *angiotensin II*, which also causes ADH release by stimulating the organum vasculosum of the lamina terminalis (see above). **Opposite effects occur in hypervolemia.**

The high pressure receptors act in a similar way as the low pressure receptors, but they regulate release of ADH *only if the changes in ECF volume are great enough to affect the arterial blood pressure*.

ADH is also released **on standing** (because the blood pools in the legs and the low pressure receptors monitor a decrease in the ECF volume). However, **hemorrhage is the most potent stimulus for ADH release** which helps rise of the blood pressure (by its V.C. and fluid retention effects).

3. Other factors : A wide variety of conditions affect the release of ADH e.g. it is released by pain, nausea, exercise, some emotions & surgical stress.

4. Drugs : The release of ADH is affected by certain drugs e.g. it is stimulated by morphine and nicotine while it is inhibited by alcohol.

DIABETES INSIPIDUS

This is a disease caused by **ADH deficiency** as a result of damage of the **ADH-secreting hypothalamic nuclei** by disease. *The body of the neurohypophysis is not essential for secretion of its hormones* (opposite to the adenohypophysis) and its removal produces only temporary symptoms because the sectioned nerve fibres will recover and secrete ADH again.

Some cases are due to *inability of the kidneys to respond to ADH* (= **nephrogenic diabetes insipidus**) because of either *congenital defects in the V_2 receptors or mutations in the gene that produces the aquaporins*. The main symptoms of the disease are the following :

1. Polyuria : This is excretion of large amounts of urine (15-20 litres daily) that is almost colourless and much diluted (due to reabsorption

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of solutes) having a low specific gravity (1002-1006) and is often accompanied by *loss of the water-soluble vitamins*.

2. **Polydipsia** : This is drinking of large amounts of water as a result of an *excessive sensation of thirst* (caused by the dehydration due to polyuria). *The sensation of thirst in this condition is life-saving.*

The main differences between diabetes insipidus and diabetes mellitus are summarized in the following table (see pages 94 and 95) :

	Diabetes insipidus	Diabetes mellitus
Polyuria, polydipsia and thirst	Severe	Less severe
Glucosuria	Absent	Present
Urine specific gravity	Very low (1002-1006)	High (1030 or more)
Urine colour	Colourless	Lemon yellow
Urine pH	Almost neutral (due to excess water diuresis)	Acidic (due to presence of keto-acids.

Syndrome of inappropriate hypersecretion of ADH (SIADH)

Hypersecretion of ADH sometimes occurs in patients having certain *cerebral diseases*. It was also encountered in certain *pulmonary diseases* particularly *cancer of the lung*. In the latter condition, the syndrome may be due to either excessive ADH secretion from the tumour, or interruption of the afferent vagal nerve fibres from the stretch receptors in the atria and great veins that transmit inhibitory signals for the secretion of ADH.

Effects of SIADH

The main effect of SIADH is *excessive water retention in the body* which leads to the following :

1. **Signs of water intoxication** (refer to blood).
2. **A marked increase in the ECF volume**. This results in the following :
 - a) *Reduction of Na^+ concentration and osmolality of the ECF.*
 - b) *Inhibition of secretion of the aldosterone hormone.* This leads to Na^+ loss in the urine (so the condition is sometimes called *cerebral or pulmonary salt wasting*), and the resulting *hyponatremia* further decreases the plasma Na^+ concentration (from 135-145 to 110-120 mEq / litre) which produces characteristic signs and symptoms (refer to kidney) and frequently causes *sudden death*.

Treatment of SIADH

1. Treatment of the cause if detected, e.g. if the cause is an ADH –secreting tumour, removal of the tumour would improve the condition.
2. Drugs that produce diuresis, induce partial renal damage, inhibit ADH secretion or reduce the renal response to ADH e.g. (the antibiotic demeclocycline).
3. Water restriction.

OXYTOCIN

This is a 9 amino acid polypeptide that is secreted mainly by the *paraventricular nucleus of the hypothalamus* (page 27) and is stored in the neurohypophysis. Its action on the target cells is mediated by increasing the intracellular Ca^{2+} content (page 9).

EFFECTS (FUNCTIONS OR ACTIONS) OF OXYTOCIN

(1) MILK EJECTION : This is the *most important function of oxytocin* in mammals. The hormone causes contraction of special smooth muscle fibres around the ducts of the mammary glands known as the *myoepithelial cells*, thus squeezing milk outwards through the nipples (page 146).

(2) CONTRACTION OF THE MYOMETRIUM (= UTERINE MUSCLE) :

Oxytocin causes contraction of the myometrium of *both the pregnant and non-pregnant uterus*. During intercourse, oxytocin is released leading to uterine contractions which produce *the sensation of orgasm* in the female and help *the transport of sperms upwards in the female genital tract*. In the pregnant uterus, *oxytocin (which is also locally produced in the uterus)* plays an important role in *labor* (page 143).

(3) CONTRACTION OF SMOOTH MUSCLE IN THE MALE INTERNAL GENITALIA : This causes *discharge of sperms from the seminiferous tubules and epididymis to the vas deferens and from the later to the urethra, which helps emission of semen*.

(4) INVOLUTION (DEGENERATION) OF THE CORPUS LUTEUM :

In some domestic animals (and probably also in humans), this process (also called *luteolysis*) is induced by *prostaglandins formed under influence of oxytocin that is locally-secreted by the corpus luteum itself* (page 120).

FACTORS AFFECTING OXYTOCIN SECRETION

1. Tactile stimulation of the nipples and surrounding areas of the breast : This occurs during suckling, and it stimulates *oxytocin* and *prolactin* secretion in lactating women which leads to both milk secretion & milk ejection (page 146). This mechanism is a *neuroendocrine reflex* called the *suckling reflex* (figure 13).

2. Distension or stretch of the cervix of the uterus : This occurs during labor, and it leads to oxytocin secretion which causes uterine contractions, thus helping delivery of the baby (page 143).

3. Stimulation of the genital organs : This occurs during sexual intercourse, and it leads to oxytocin secretion *in both sexes*. In females, it produces uterine contractions that cause transport of the sperms up (thus helping the process of fertilization), while in males it helps emission of semen (see above).

4. Other factors : The secretion of oxytocin is altered by many emotional and stressful stimuli, inhibited by alcohol and stimulated through *conditioned reflexes* e.g. it is secreted when a mother thinks in her baby or hears him crying (page 146).

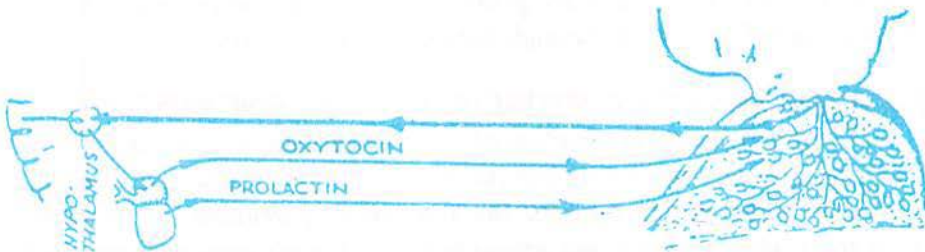


Figure 13 : The suckling reflex.

Mechanism of oxytocin secretion in various conditions

Signals from the nipples (in case of suckling), from the genital organs (during intercourse) and from the uterine cervix (during labour) are discharged to the spinal cord from which signals are then transmitted upwards to the hypothalamus, where they stimulate the paraventricular nucleus leading to release of oxytocin from the neurohypophysis as described above.

CHAPTER 3

THE THYROID GLAND

The thyroid gland is located in the front of the neck below the larynx on either side of the trachea. It is formed of 2 lobes connected by a narrow isthmus, and sometimes there is a small pyramidal lobe arising from the isthmus (figure 14). Histologically, the gland is made up of spherical acini called the *thyroid follicles*. Each follicle is lined by a single layer of epithelial cells (which are cuboidal in the euthyroid state) and is surrounded by a dense network of fenestrated capillaries. The lumens of the follicles are filled with a protein material called *colloid*, and in between them there are special cells called the *clear (or C) or parafollicular cells* (figure 15).

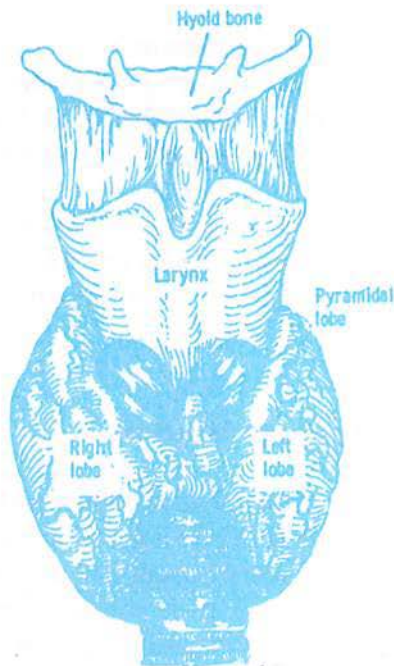


Figure 14 : The human thyroid gland (anterior view).

When the gland is inactive, the colloid is abundant, the follicles are large and the cells lining them are flat. On the other hand, when the gland is active, the follicles are small, the cells enlarge (becoming columnar) and the colloid is decreased and its edge becomes scalloped forming many small *re-absorption lacunae* (figure 15).

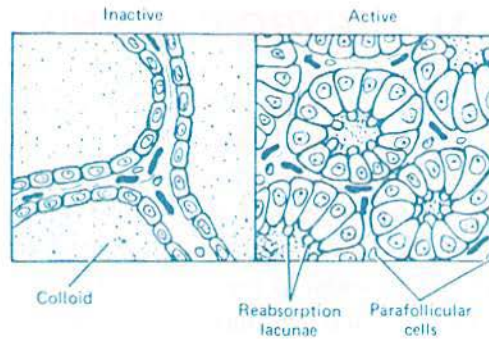


Figure 15 : Histology of the thyroid gland. Inactive (left) and active (right).

THE THYROID HORMONES

1. **Thyroxine** (= Tetraiodothyronine or T_4).
2. **Triiodothyronine** (= T_3) and a small amount of an inactive compound called *reverse triiodothyronine* (RT_3). Under normal conditions the gland secretes *daily* about 80 mcg (micrograms) of T_4 , 4 mcg of T_3 and 2 mcg of RT_3 .
3. **Calcitonin** (formerly *thyrocalcitonin*) : This is a polypeptide hormone that is secreted by the *parafollicular cells*. It is a *calcium-lowering hormone* that is discussed with the parathyroid glands (chapter 6).

IODINE METABOLISM

Daily requirement and supply of iodine

The minimal daily requirement of iodine which maintains a normal thyroid function is about 2 mcg / kg of body weight (*about 150 mcg daily*), but the usual intake is much greater (about 500 mcg daily). Iodine is rich in areas *near the sea*, and it enters the body with food and water. Subjects who live in areas away from seas (eg. the oases and central Europe) are protected from iodine lack by adding sodium iodide to table salt (*iodized table salt*).

Fate of iodine

The ingested iodine is converted to iodide then it is absorbed from the small intestine. When 500 mcg are ingested, the thyroid gland takes up only 120 mcg (at the normal rate of function) while 380 mcg remain in the plasma. The gland secretes 80 mcg in the form of T_3 and T_4 , while 40 mcg

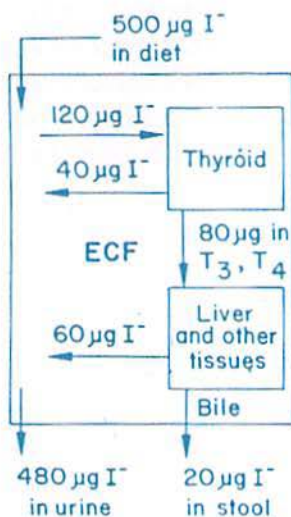


Figure 16 : Iodine metabolism.

diffuse into the plasma. The secreted hormones are metabolized in the liver (and other tissues) and their iodide content is released. About 60 mcg enter the plasma while 20 mcg are excreted in bile and lost in feces. The iodide in the plasma will be, therefore, 480 mcg (380 + 40 + 60), and this will be excreted in urine (figure 16).

Synthesis and secretion of thyroid hormones

1. Iodide trapping (= iodide pump) : This is an active process by which iodide is taken by the thyroid gland cells from the plasma, and is the *first step in synthesis of the thyroid hormones*. Iodide is transported into the thyroid follicular cells with Na⁺ by a *secondary active transport mechanism* using a carrier called *NIS (Na⁺ - I Symport)* and the energy is provided by Na⁺-K⁺ATPase activity. Iodide then moves into the colloid by diffusion (possibly along I⁻ channels). This symport can produce intracellular I⁻ concentrations that are 20-40 times as great as the concentration in the plasma and still iodide is actively transported from the serum into the thyroid cells against both the concentration and electrical gradients for I⁻ ..

2. Oxidation of iodide to iodine : After iodide trapping, it is oxidized in the colloid to *iodine* by activity of the *thyroid peroxidase enzyme*.

3. Binding of iodine to tyrosine : Iodine is then bound to tyrosine forming *mono-iodotyrosine (MIT)*, which is further iodinated forming *di-iodotyrosine (DIT)*, and both **MIT and DIT are biologically inactive**.

Such *iodination reactions* are also catalyzed by the thyroid peroxidase enzyme and they occur in the colloid by combination of I^- with the tyrosine residues that are part of a large glycoprotein molecule (m.w. 660000) called **thyroglobulin** (figure 17). Both the thyroid peroxidase enzyme as well as thyroglobulin are synthesized by the follicular cells then secreted into the colloid by *exocytosis*.

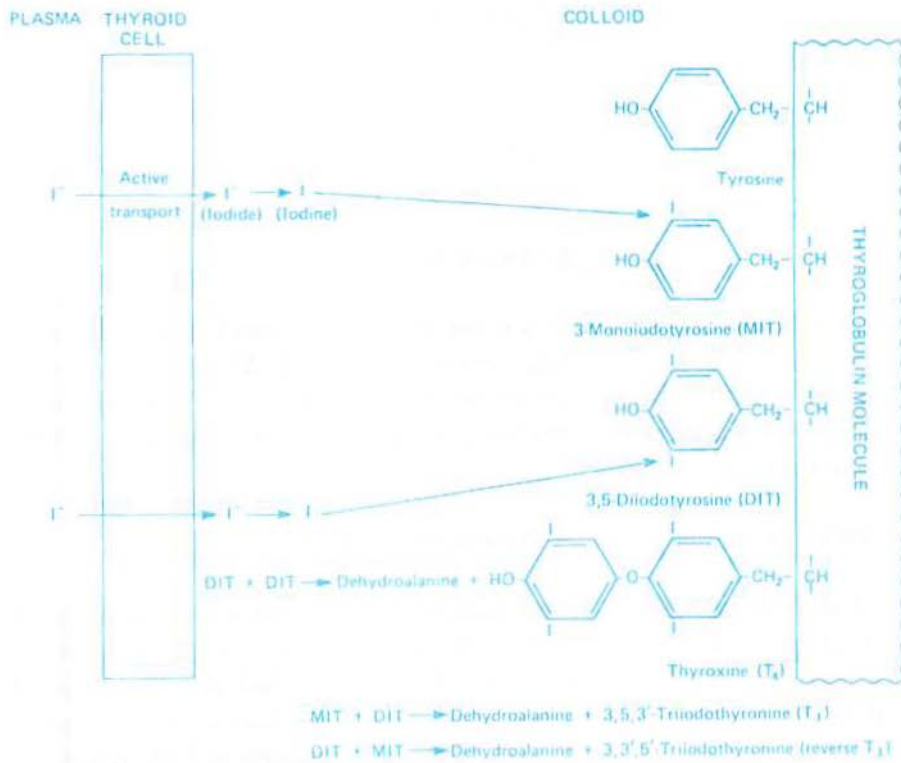


Figure 17 : Synthesis of the thyroid hormones.

4. Condensation (coupling) of MIT and DIT : 2 DIT molecules undergo an oxidative condensation forming T_4 . T_3 is formed by condensation of MIT with DIT, and a small amount of RT_3 is also formed. Such coupling reactions are probably also catalyzed by the thyroid peroxidase enzyme.

5. Secretion of the thyroid hormones : The hormones remain bound to thyroglobulin till they are secreted. When the gland secretes, the follicular cells ingest the colloid by endocytosis, producing the *reabsorption lacunae*

(figure 15). In the lysosomes, the peptide bonds between the iodinated compounds and thyroglobulin are broken by *protease enzymes* leading to release of these compounds into the cytoplasm. The iodinated tyrosines (MIT and DIT) are deiodinated by the *iodotyrosine deiodinase enzyme* and the iodide liberated is re-used in hormonal synthesis. However, this enzyme *does not attack the iodinated thyronines* (T_3 and T_4), which will pass into the bloodstream. In normal conditions, small amounts of the colloid and thyroglobulin also enter the bloodstream, but their functions in the body are unknown.

**** The thyroid cells exert 3 functions :** (1) They collect and transport iodide (2) They synthesize thyroglobulin then secrete it (with the thyroid peroxidase enzyme) in the colloid (3) They ingest the thyroglobulin, separate the hormones and then secrete them into the bloodstream.

****** The salivary glands, gastric mucosa, placenta, ciliary body, choroid plexus (in the brain) and the mammary glands also transport iodide against a concentration gradient. The mammary glands also bind iodine, and DIT is formed but T_3 and T_4 are not. However, unlike the thyroid gland, such processes in these organs are not stimulated by TSH.

Transport and concentration of the thyroid hormones

The normal total plasma T_4 level is about 8 mcg % and that of T_3 is about 0.15 mcg % (while the normal inorganic iodide plasma level averages 0.3 mcg %). Both hormones are present in 2 forms, *the majority is bound to plasma proteins, while a very small fraction is present free.*

The plasma proteins that bind the hormones are mostly *albumin*, a *prealbumin* called *transthyretin* and a *thyroxine-binding globulin*. The *free hormones are the physiologically active hormones*, and constitute the fraction capable to inhibit TSH secretion. The *protein-bound fraction acts as a store (or reservoir)* for the hormones, and is normally in equilibrium with the free fraction (aiming at maintaining the level of the free hormones constant). The amounts of the protein-bound and free fractions of the thyroid hormones are as follows :

1. T_4 : About 99.98 % is bound and 0.02 % is free.
2. T_3 : About 99.80 % is bound and 0.20 % is free.

It is clear that T_3 is *less bound*, thus it has a shorter half-life, its biological activity is 3-5 times greater and its action is much more rapid than T_4 . It is believed that T_4 is *changed to T_3 in the cytoplasm of the target cells.*

Mechanism of action & metabolism of the thyroid hormones

The thyroid hormones bind to *specific nuclear receptors* in the target cells and exert their effects by increasing *transcription of mRNAs* (figure 2). They are then inactivated in the following ways :

1. Deiodination (by 3 different *deiodinase enzymes*). : This occurs in the liver, kidneys and many other tissues. Normally about 1/3 of T_4 is converted to T_3 (see above) and 45 % is converted to RT_3 (most of the circulating T_3 and RT_3 are formed by deiodination of T_4). T_3 and RT_3 are then further deiodinated and broken down to tyrosine and iodide (which is re-used by the thyroid gland in the synthesis of thyroid hormones).

2. Conjugation : In the liver, T_4 and T_3 are conjugated to form sulphates and glucuronides, which are then *excreted in the bile*. In the intestine, the thyroid conjugates are hydrolyzed, and some of the hormones are reabsorbed while some are excreted in the stool.

Actions (functions or effects) of the thyroid hormones

1. Calorigenic effect : The thyroid hormones *increase the metabolic rate and O_2 consumption* in all tissues (except the adult brain, testes, uterus, lymph nodes, spleen and anterior pituitary gland). This effect increases heat production and body temperature, and is partly due to increased metabolism of fatty acids (since the hormones stimulate lipolysis in adipose tissue) and partly due to increased activity of the membrane bound $Na^+ - K^+$ ATPase.

2. Effects on the heart : The thyroid hormones *increase the myocardial contractility* (by stimulating formation of *alpha myosin heavy chains* which have high $Na^+ - K^+$ ATPase activity). They also *increase the number of beta adrenergic receptors and enhance the responses to catecholamines*. Accordingly, *the heart rate, stroke volume, cardiac output and systolic B.P. are increased*. Such effects lead to *increase of the pulse pressure, shortening of the circulation time and liability to develop arrhythmias e.g. extrasystoles and atrial fibrillation* (due to increased cardiac excitability).

3. Effects on the nervous system : The thyroid hormones are essential for the *normal development of the nervous system* (so in hypothyroid infants the synapses develop abnormally, myelination is defective, the reflex reaction time is prolonged, and mental development is retarded).

4. Effects on growth : The thyroid hormones promote bone growth & skeletal development early in life (with other hormones) and are also essential for growth afterwards by exerting a *permissive action to the growth*

hormone They also affect teeth growth, the contours of the face and the proportions of the body (page 22). They also exert *a direct effect on tissue maturation* e.g. tadpoles treated with thyroid hormones metamorphose early into dwarf frogs, while those deprived from these hormones never become frogs.

5. Effects on respiratory functions : The thyroid hormones help O_2 dissociation from haemoglobin by increasing the amount of 2, 3 diphosphoglycerate (DPG) in the R.B.C.s. (refer to respiration).

6. Effects on sex functions : Sex functions are stimulated by the thyroid hormones. They are essential for *normal menstrual cycles and spermatogenesis*, and also *increase milk secretion* in lactating women.

7. Conversion of carotene to vitamin A in the liver : If the thyroid hormones are deficient, *carotenemia* results. This causes *yellowish colouration of the skin*, but unlike jaundice the colour of the sclera is not altered.

8. Effects on protein metabolism and skeletal muscles : The thyroid hormones cause *protein catabolism* and -ve nitrogen balance, so in hyperthyroidism, bone demineralization, osteoporosis & muscle weakness occur.

9. Effects on carbohydrate metabolism : The thyroid hormones increase the rate of carbohydrate absorption from the G.I.T., thus *the blood glucose level increases after a carbohydrate meal*. However, it normally falls again rapidly because glucose utilization in the tissues also increases.

10. Effects on lipid and cholesterol metabolism : The thyroid hormones *lower the blood cholesterol level* by increasing formation of low-density lipoprotein (LDL) receptors in the liver, which favour hepatic removal of cholesterol from the blood. They also lower the blood level of lipids (although they stimulate lipolysis in adipose tissue) because they simultaneously increase the metabolism of the fatty acids (see above).

Relation between the thyroid hormones and catecholamines

The actions of the thyroid hormones and those of catecholamines are *synergistic and closely interrelated*. Like thyroxine, epinephrine increases the metabolic rate (calorigenic action), stimulates the nervous system and produces similar cardiac effects (but for a shorter duration). Accordingly, the toxicity of catecholamines is markedly increased in rats treated with T_4 . Many of the effects produced by the thyroid hormones seem to be mediated through *increasing the tissue responsiveness to catecholamines specially stimulation of the nervous system and the cardiac effects*. This is proved by the fact that in hyperthyroidism, many of the symptoms are improved after sympathectomy. The cardiac effects are also improved by *beta adrenergic blocker drugs e.g. propranolol*.

Control (regulation) of thyroid gland activities

The synthesis and secretion of the thyroid hormones is controlled by the *thyroid stimulating hormone (TSH)* as well as by the *dietary iodine intake*

(A) TSH (or thyrotropin)

This hormone (which is secreted by the thyrotrope cells of the adenohypophysis) is a *glycoprotein that entirely controls the activity of the thyroid gland* by increasing the intracellular content of *cyclic AMP* (so after hypophysectomy, the thyroid gland atrophies). Its normal plasma level averages *2 microunits / ml* and it exerts a generalized stimulating effect on the thyroid gland leading to :

(1) **A marked increase in** (a) The size of the follicular cells (becoming columnar) (b) The vascularity and activity of the gland (so the rates of iodide pump and iodine binding, synthesis and secretion of thyroglobulin as well as the release of the hormones are all increased).

(2) Generalized enlargement of the gland (= **goiter**).

****** In addition to the TSH receptors, the thyroid cells also contain receptors for IGF 1 which promotes their growth.

Factors that control TSH secretion

1. Thyrotropin-releasing hormone (TRH) : This is one of the *hypophysiotropic hormones* secreted by the hypothalamus. Like TSH, it acts through increasing the *cyclic AMP content of the thyrotropes* leading to secretion of TSH. It is liberated in certain conditions e.g. exposure to cold (specially in infants).

2. Feedback control : There is a *negative feedback* relation between the plasma level of the *free part of the thyroid hormones and the release of TSH* i.e. when the free blood hormonal level increases (specially T_3), the release of TSH decreases and vice versa. This mechanism maintains a constant hormonal blood level, and it acts at both the hypothalamic as well as the pituitary levels (figure 8).

3. Other factors :

- (a) Dopamine, somatostatin and glucocorticoids inhibit TSH secretion.
- (b) The secretion of TSH shows a *circadian rhythm*, its mean output starts to rise at about 9 PM, peaks at midnight, then declines during the day.
- (c) During pregnancy, the placental hormone *hCG* (page 137) activates

the thyroid receptors leading to mild hyperthyroidism and enlargement of the thyroid gland (goiter). In this case, the secretion of the pituitary TSH may be depressed. It was reported that the placenta also secretes a thyroid stimulator other than hCG, and it was called *human chorionic thyrotropin* (page 140).

(B) Dietary iodine intake

An adequate dietary iodine intake is essential for normal thyroid function. When the intake falls below 50 mcg/day, the synthesis and secretion of the thyroid hormones are decreased and as a result, the secretion of TSH increases leading to thyroid enlargement (goiter). Such *iodine-deficiency goiter* can be corrected by iodine administration in diet.

On the other hand, when iodides are present in the blood in high concentrations, the vascularity and all activities of the thyroid gland are decreased and consequently, the release of the thyroid hormones is also decreased. This effect is known as the *Wolff-Chaikoff effect*, and it occurs because the excess iodide (a) Decreases the organic binding of iodine in the thyroid gland (b) Reduces the effect of TSH by reducing the cyclic AMP response to this hormone (c) Inhibits proteolysis of thyroglobulin.

****** The *Wolff-Chaikoff effect* is greater and more prolonged when the iodide transport is increased. This is why patients with hyperthyroidism are more responsive to iodide than normal individuals, and before the operation of thyroidectomy, these patients are treated with iodide salts to decrease the size and vascularity of the gland, thus the surgery becomes easier and the blood loss is minimized.

Antithyroid substances and drugs

1. Excess iodide salts : These depress the activity of the thyroid gland, so when given to hyperthyroid patients, temporary improvement occurs.

2. Perchlorate and chlorate anions : These and certain other *mono-valent anions* (e.g. pertechnetate, nitrate, periodate and biiodate anions) decrease iodide trapping in the thyroid gland by *competitive inhibition* (they compete with iodide for transport into the gland via the $\text{Na}^+ - \text{I}^-$ symport). Thiocyanate (another monovalent anion) also inhibits iodide transport but it is not concentrated in the gland (so *perchlorate is about 10 times more active than thiocyanate*).

3. Thiourylenes : These are a group of compounds related to thio-urea (e.g. *propylthiouracil and methimazole*). These drugs (a) *Inhibit organic binding of iodide* because they compete with tyrosine for iodine

and become iodinated instead **(b) Block the coupling reactions** that form T_3 and T_4 . Propylthiouracil also inhibits conversion of T_4 into T_3 in extra-thyroidal tissues (by blocking the deiodinase enzyme). In hyperthyroidism, these drugs may also improve the symptoms by inhibiting the immune system, which decreases the formation of stimulatory antibodies (see below).

4. Naturally-occurring goitrogenic substances (goitrogens) : Certain vegetables (specially *cabbage and turnips*) contain antithyroid substances called **goitrogens** (because they decrease the thyroidal hormonal blood level, so TSH is excessively secreted leading to goiter). These vegetables contain an *inactive* goitrogen called **progoitrin**, and an *activator* that converts progoitrin to active goitrin. This activator is heat-labile, but when destroyed by cooking, goitrin is still formed because there are other activators in the intestine (probably of bacterial origin). On normal mixed diets, the goitrin intake is usually not enough to produce goiter, but in vegetarians "*cabbage goiters*" do occur. Other plant goitrogens probably exist and may be responsible for the small **goiter epidemics** that are reported every now and then from various parts of the world.

GOITER

Goiter is **a thyroid enlargement that is non-inflammatory and non-malignant** (i.e. not due to tumours). It is **3 types** :

(A) Simple goiter

This is associated with **normal thyroid function (euthyroidism) and histological structure**. It occurs due to either *mild iodine deficiency* or normally during puberty (in which there is increased need for iodine) producing **physiological goiter**. In such cases, the blood level of the thyroid hormones is initially decreased, so excessive TSH is secreted leading to thyroid enlargement. Simple goiter may also occur **during pregnancy** (see above).

(B) Colloid goiter

This is associated with **hypothyroidism and the follicles are enlarged and lined by flat cells** (figure 15). The condition results from *severe iodine deficiency*, and its mechanism is similar to that of simple goiter, except that TSH stimulates the thyroid cells to secrete large amounts of colloid, *but the synthesis and secretion of the thyroid hormones do not increase due to lack of iodine*, resulting in goiter together with symptoms of hypothyroidism (= **iodine deficiency goiter**).

****** In the areas that are *deficient in iodine* e.g. central Europe (which is far from seas) and the area around the great lakes in USA (in which *the soil is deficient in iodine* by the effect of rain), iodine deficiency goiter prevailed in the past (*before using iodized table salt*) and was thus called *endemic goiter*.

(C) Toxic goiter

This is associated with *hyperthyroidism*, and the *follicular cells become columnar* while the follicular lumens are decreased in size and contain smaller amounts of colloid than normal (figure 15). It is due to excessive stimulation of the thyroid gland and is known as *Graves' disease* (page 46).

DISORDERS (DISEASES) OF THE THYROID GLAND

[I] Hypothyroidism (myxedema and cretinism)

(A) Myxedema (= hypothyroidism in adults)

The common causes of myxedema include the following :

1. Damage of the thyroid gland as a result of disease e.g. cancer (= *primary hypothyroidism*).
2. Deficient TSH secretion due to either pituitary or hypothalamic disease (= *secondary hypothyroidism*).

Manifestations (symptoms) of myxedema

(1) *Skin changes* : The skin becomes *dry, scaly and yellowish* (due to *carotenemia*) and hair falls (becoming coarse and scanty). There is generalized *nonpitting edema* but specially in the face, producing characteristic puffiness (figure 18). This is due to subcutaneous accumulation of a *waxy-like myxematous tissue* (which is formed of proteins, polysaccharides, hyaluronic acid, chondroitin sulphuric acid and water).

(2) *The basal metabolic rate (B.M.R.) is decreased*, and the patient *cannot tolerate cold weather*. The decreased B.M.R. together with the myxematous tissue lead to *an increase in the body weight* although there is decreased appetite and food intake.

(3) *The muscles become weak and easily fatigued* and there is also muscle cramps and stiffness.

(4) *Nervous symptoms* : Mental functions are depressed, so the patient's thinking becomes slow and his memory poor. *Somnolence* is marked and

facial expression becomes dull, so the patient looks *apathetic*. In some patients, there are severe mental symptoms (= *myxedema madness*).

(5) *The patient's voice becomes husky and slow* (so myxedema is probably the only disease that can be *diagnosed over the telephone*).

(6) The blood cholesterol level (normally 150-250 mg %) is increased (= *hypercholesterolemia*) and this predisposes to *atherosclerosis*.

(7) *Depression of sex functions* (so spermatogenesis is depressed in male patients and amenorrhea may occur in female patients).

(8) There may also be *hypochromic microcytic anaemia* (due to depression of the metabolic processes in the bone marrow).



Figure 18 : The face in case of myxedema (note puffiness and falling of hair).

(B) Cretinism (= hypothyroidism in youngs)

Children who are hypothyroid from birth are called **cretins** (figure 19). The condition is usually due to either :

1. Maternal causes, commonly maternal iodine deficiency or maternal antithyroid antibodies that cross the placenta and damage the fetal thyroid gland.
2. Fetal causes e.g. fetal thyroid gland maldevelopment, fetal hypopituitarism or inborn errors of thyroid hormone synthesis.

Manifestations (symptoms) of cretinism

- (1) **Delayed physical growth :** During infancy, all features of growth are delayed (e.g. teeth eruption, sitting, walking and closure of the skull fontanelles). Later, there is failure of proliferation of epiphyseal cartilages, so the *cretin is a dwarf* having a height not exceeding one meter (fig. 19).
- (2) **Mental retardation :** The cretin may be a *complete idiot*. There are also speech defects as well as urine and feces incontinence.
- (3) **Low B.M.R.** (so the cretin *cannot tolerate cold weather*).

(4) The skin is thick and dry, the hair is coarse and scanty, and the nails are brittle. Skin thickening is due to subcutaneous overgrowth of soft tissue, and it gives the patient an obese appearance.

(5) **Sexual retardation** : Sexual development and puberty are delayed (page 102) and sexual maturation may be completely arrested (leading to *impotence in males and amenorrhea in females*).

(6) **General features** : In the face, the eyelids are swollen *with narrowing of the palpebral fissure*, the nose is depressed with wide nostrils, and the tongue is enlarged and protrudes between thick lips. There is also *bulging abdomen* and frequently umbilical hernia (figure 19).

Treatment of myxedema and cretinism

Myxedema is treated by thyroid hormones. However, TSH is useful in cases due to pituitary disease while TRH is useful in cases secondary to hypothalamic disorders. On the other hand, in cases of cretinism, unless the mother was severely hypothyroid, all symptoms can be *prevented by giving thyroid hormones*, provided that the treatment is started *soon after birth* (but once the typical picture has developed, it is usually too late for the treatment to be effective, particularly in preventing mental retardation which is irreversible).



Figure 19 : A cretin (note dwarfism, bulging abdomen and facial changes).

[II] Hyperthyroidism (thyrotoxicosis) & Graves' disease

Hyperfunction of the thyroid gland may occur as a result of tumours in the gland itself or TSH-secreting pituitary tumours. However, the most common cause of thyroid overactivity (60-80 % of cases) is **Graves' hyperthyroidism or disease (or exophthalmic goiter)**. This is an **autoimmune disease** in which abnormal antibodies are formed. Opposite to may be expected, these antibodies **stimulate the TSH receptors** in the thyroid gland. They were called *thyroid-stimulating immunoglobulins (TSI)* or *long-acting thyroid stimulators (LATS)* but now they are called **TSH receptor-stimulating antibodies (TSH-R-stim-Ab)**.



Figure 20 : The face in Graves' disease (note the goiter and exophthalmos).

Manifestations (symptoms) of Graves' disease

(1) The thyroid gland is diffusely enlarged, and since there is also exophthalmos, the disease is called **exophthalmic goiter** (figure 20).

(2) **Increased B.M.R.** (from +10 % up to +100 %) so there is excessive sweating (to increase the heat loss) and the patient's skin is always **moist, warm and flushed** (i.e. red) due to V.D. This is associated with **heat intolerance**.

(3) **Cardiovascular symptoms :** These include tachycardia and palpitation, increased cardiac output and systolic B.P., *extrasystoles and atrial fibrillation* in some cases. The diastolic B.P. is not changed or decreased

(due to the cutaneous V.D.) so the *pulse pressure increases leading to water hammer (collapsing) pulse*. The cardiac muscle may also suffer *relative ischemia* due to its increased demand of blood supply. In some cases, the cardiac output is increased but is still inadequate to maintain tissue perfusion due to the increased B.M.R., leading to "**a high output failure**".

(4) **Nervous symptoms** : There is increased excitability of the nervous system (probably as a result of *increased responsiveness of the reticular formation to catecholamines*). This is shown by nervousness, irritability, anxiety, restlessness, insomnia and *fine tremors of the outstretched fingers*.

(5) **Metabolic changes** : Hyperglycemia (and may be glucosuria) and a *decrease in the serum cholesterol level* (below 120 mg %).

(6) Increased food intake (= **hyperphagia**) associated with weight loss due to the excessive metabolism.

(7) **Increased intestinal movements** and *may be diarrhea*.

(8) **Increased protein catabolism** : In bones, this leads to *demineralization and osteoporosis* associated with *hypercalcemia and hypercalcuria*. The skeletal muscles become weak & easily fatigued (*thyrotoxic myopathy*) due to loss of creatine, which is excreted in urine resulting in *creatinuria*.

(9) **Exophthalmos** : This is forward protrusion of the eyeballs and is usually associated with *eye lid retraction*. It is an early sign of the disease and it occurs in 50 % of cases. It is due to swelling of the orbital tissues (the connective tissue and extraocular muscles) which pushes the eyeballs forward. It is believed that fibroblasts that contain TSH receptor protein develop in the orbits and these cells are stimulated by the *TSH-R-stim-Ab* and in response they release certain *cytokines* that promote inflammation and edema of the orbital tissues, leading to forward eyeball protrusion.

Treatment of Graves' disease

1. Giving *antithyroid drugs* e.g. propylthiouracil (page 41).
2. Giving *radioactive iodine* (^{123}I) in certain doses that damage some of the overactive thyroid cells.
3. Surgical removal of a part of the thyroid gland (= *subtotal thyroidectomy*).

THE THYROID FUNCTION TESTS

[A] SPECIFIC TESTS

(1) **Measurement of PBI (Protein-Bound Iodine)** : The normal value of PBI is *4 - 8 mcg %*. It increases in hyperthyroidism and decreases in hypothyroidism. However, it is **not conclusive** in the diagnosis of

thyroid diseases because the amounts of the thyroid binding proteins vary normally by various factors, and consequently high or low values of PBI may be found in individuals with euthyroid (= normal thyroid) activity.

(2) Measurement of the total thyroid hormonal blood level : In spite of the higher values than normal found in thyrotoxicosis and the lower values found in myxedema, yet as the PBI, it is also **not conclusive** in the diagnosis since high or low values may be found in normal individuals.

(3) Estimation of radioactive iodine uptake by the thyroid gland : The iodine uptake by the thyroid gland is a good index of its function. A tracer dose of a radioactive iodine e.g. ^{131}I (or better ^{123}I) that has no damaging effects on the gland is administered and the thyroid uptake is determined. In hyperthyroidism, the iodine uptake is more than normal, while in hypothyroidism it is less than normal.

(4) TSH stimulation test : This test *differentiates between primary and secondary hypothyroidism*. A test dose of TSH is injected, then *the thyroid hormonal blood level is measured*. It increases in cases of secondary hypothyroidism and not affected in cases of primary hypothyroidism.

(5) TRH stimulation test : This test *differentiates between pituitary and hypothalamic lesions* in cases of *secondary hypothyroidism*. A test dose of TRH is injected, then *the plasma TSH level is measured*. It increases in cases due to hypothalamic lesions but it is not affected in cases due to pituitary lesions.

(6) Estimation of the plasma free T_3 & T_4 and TSH levels : This is accurately done now (by radioimmunoassay), and is *the most reliable method for assessing thyroid function*. *The free thyroid hormonal blood level is decreased in hypothyroidism and increased in hyperthyroidism*. On the other hand, *the TSH level is increased in hypothyroidism and decreased in hyperthyroidism (if the disease is due to a thyroid disorder)*.

[B] NONSPECIFIC TESTS

(1) Determination of the basal metabolic rate (B.M.R.) : Normally, it averages 40 ± 15 % kilocalories/ sq.m/ hour in adult males (refer to metabolism). It *increases in hyperthyroidism and decreases in hypothyroidism*.

(2) Determination of the serum cholesterol level (normally about 200 mg %). It *increases in hypothyroidism and decreases in hyperthyroidism* (however both B.M.R. and serum cholesterol are affected by many other factors, so they are not specific in diagnosis of thyroid disorders).

CHAPTER 4

THE ADRENAL (SUPRARENAL) CORTEX

There are 2 adrenal glands (each weighing 4-5 gm in adults), one at the superior pole of each kidney (figure 1). Each gland consists of 2 separate endocrine tissues that are different structurally and developmentally as well as functionally. The inner part is the adrenal medulla (about 28 % of the mass of the gland), while the outer part is the adrenal cortex (about 72 % of the mass of the gland) which is *essential to life* (page 2).

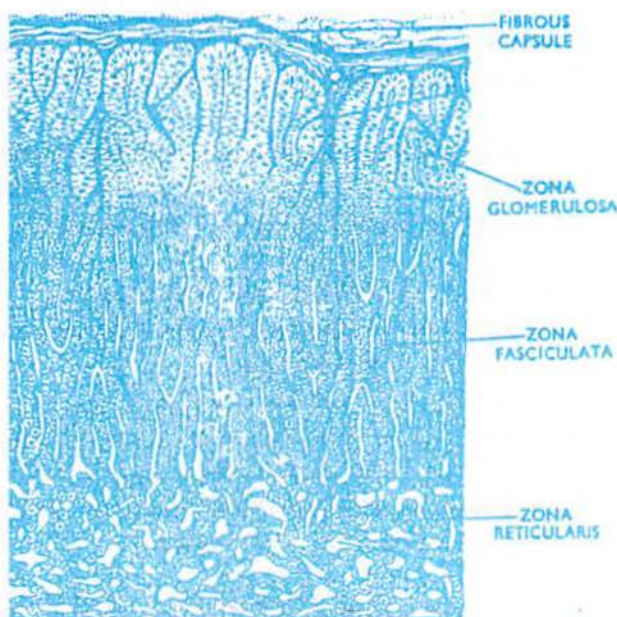


Figure 21 : Structure of the adrenal cortex.

Functional histology of the adrenal cortex

The adrenal cortex is formed of **3 distinct zones** (figure 21) :

1. **Zona glomerulosa** : This is the outer zone and it constitutes about 15 % of the mass of the gland. The cells of this zone are *able to form new cells that regenerate the other zones*.
2. **Zona fasciculata (fasciculosa)** : This is the middle zone. It is the largest zone since it constitutes about 50 % of the mass of the gland.
3. **Zona reticularis** : This is the inner zone. It is the smallest zone since it constitutes only about 7 % of the mass of the gland.

The cells of the adrenal cortex are rich in *cholesterol* (from which its hormones are synthesized) and contain large amounts of *smooth endoplasmic reticulum and mitochondria* (in which synthesis of the hormones takes place).

All adrenocortical hormones contain a steroid ring (so they are called *corticosteroid hormones*). They are 2 types : *C₂₁ steroids and C₁₉ steroids*. Both mineralocorticoids and glucocorticoids are *C₂₁ steroids* (see below) while *C₁₉ steroids* have an androgenic activity and most of them include a keto group at position 17 (so they are also called *17-ketosteroids*).

Rate of secretion of the corticosteroids

Corticosterone is synthesized in the 3 zones of the gland, and is the precursor of all secreted hormones which include the following :

- (1) From zona glomerulosa : 2 mineralocorticoid hormones :
 - a. *Aldosterone* (formed from corticosterone at about 0.15 mg per day).
 - b. *Deoxycorticosterone (DOC)* (about 0.2 mg per day).

- (2) From both zonae fasciculata and reticularis :
 - A. 2 glucocorticoid hormones (mainly from zona fasciculata) :
 - 1- *Cortisol* (about 10 mg per day)
 - 2- *Corticosterone* (about 3 mg per day).

B. *Sex hormones* (mainly from zona reticularis) : These are mainly *androgens* (about 20 mg per day) which are mostly *dehydroepiandrosterone (DHEA) and androstenedione* (some of the latter is converted to estrogen in the circulation and certain tissues).

Plasma content and transport of the corticosteroids

The average plasma cortisol level is about *13.9 mcg %*. However, it shows *diurnal variation* (being highest in the morning and lowest at night). A very small part of the plasma cortisol is free while the majority is bound to plasma proteins [mostly to an *alpha globulin* called *corticosteroid-binding globulin (CBG) or transcortin* and a minority to *albumin*].

The average plasma concentration of corticosterone is about *0.4 mcg %* and similar to cortisol, it is mostly bound to plasma proteins.

The average plasma level of each of the mineralocorticoids is about *0.006 mcg %*, while that of each of the androgens is *175 mcg %*.

Mechanism of action & metabolism of corticosteroids

These hormones bind to specific *cytoplasmic receptors* in the target cells and exert their effects by increasing transcription of *mRNAs* (figure 2) then they are inactivated mainly in **the liver** by the following ways :

1. Most cortisol is reduced to *dihydrocortisol* then to *tetrahydrocortisol* which is conjugated to glucuronic acid and the conjugates are excreted in the urine. *Some cortisol is converted to cortisone* which is also reduced, conjugated and excreted in urine. *Cortisone is an active steroid when given as a treatment since it is converted to cortisol in the body.*

2. Most aldosterone is also converted to *tetrahydroaldosterone glucuronide* (which is also excreted in the urine).

3. The adrenal androgens and about 10 % of cortisol are excreted in urine as **17- ketosteroids**. Testosterone (which is secreted from the testes) is also converted to 17- ketosteroids and excreted in the urine. The normal urinary excretion of 17- ketosteroids *in adult females is about 10 mg/day, and in adult males 15 mg/day*. In females, all are of an adrenal origin only, while in males about 2/3 (10 mg) is of an adrenal origin while about 1/3 (5 mg) is of a testicular origin.

Functions (actions or effects) of glucocorticoids

Glucocorticoids include mainly *cortisol and corticosterone*. They are secreted *from both zonae fasciculata and reticularis* (specially the former) and they exert the following actions or effects (figure 22) :

(1) Metabolic effects

- a. **Protein metabolism** : Glucocorticoids cause *protein catabolism* (increasing the amino acid level in the blood). In the liver they increase the uptake of amino acids and their conversion into carbohydrates (*gluconeogenesis*). Protein catabolism in bones is due to increasing the osteoclastic activity and it results in (a) *Osteoporosis or osteopenia* (b) *Increased Ca^{2+} mobilization from bones* and its excretion in the urine.

- b. **Carbohydrate metabolism** : Glucocorticoids stimulate *gluconeogenesis* in the liver, and this increases both *glycogenesis in the liver* and also *the hepatic glucose output*. At the tissues, they decrease glucose uptake (*an anti-insulin action*) except in the brain and heart. Such effects lead to *hyperglycemia and may cause diabetes mellitus (steroid or adrenal diabetes)* or *worsen the diabetes if it is already present*.

c. Fat metabolism : Glucocorticoids *mobilize fat from adipose tissue and decrease hepatic lipogenesis*, thus increasing the plasma level of free fatty acids (FFAs), which are a good source of energy. The hormones also *affect the distribution of fat in the body* (see adrenocortical hyperfunction, page 61).

(2) Permissive action : The presence of glucocorticoids is important for some other hormones to exert their effects, specially for *catecholamines and glucagon* to produce their calorigenic effects, and for *catecholamines* to produce their *bronchodilator, lipolytic and pressor effects* (the latter effect of glucocorticoids is due to *increasing the vascular reactivity to catecholamines*).

(3) Effects on water & electrolyte metabolism : Glucocorticoids promote water excretion in the urine as a result of *inhibiting secretion of ADH and increasing the glomerular filtration rate*. They also stimulate *secretion of ANP* which helps urinary excretion of excess salt loads. It is to be noted that glucocorticoids also exert a *mineralocorticoid effect* (helping Na^+ retention) but such effect is *weak in the normal conditions*.

(4) Effects on blood cells and lymphatic organs : Glucocorticoids *decrease the number eosinophils, basophils & lymphocytes, and increase the number of neutrophils, platelets & red blood cells*. *Lymphopenia* is due to inhibition of lymphocyte proliferation in the lymph nodes and thymus (which leads to reduction of their sizes) as a result of inhibiting production of interleukin-2 by the T lymphocytes (refer to blood).

(5) Effects on nervous functions : Glucocorticoids influence the nervous system as evidenced by appearance of certain nervous symptoms in patients with adrenal insufficiency that are reversed only by glucocorticoids e.g. changes in the electroencephalogram and personality, irritability, apprehension and inability to concentrate.

(6) Resistance to stress : Stressful stimuli (page 55) are defined as the noxious (or injurious) stimuli that increase secretion of ACTH (through CRH secretion) leading to a rise in the plasma glucocorticoid level. This rise is essential for survival in these conditions by an unknown mechanism. However, the role of glucocorticoids in stress may be through (a) Providing substrates for extra-supply of energy specially FFAs (b) Their *permissive action to catecholamines* (see above), the liberation of which is stimulated by most stressful stimuli.

(7) Anti-inflammatory effects : Glucocorticoids suppress the inflammatory reactions by (a) Inhibiting release of the lysosomal enzymes (b) Formation of leukotrienes and interleukins (c) Decreasing the capillary

permeability. They also inhibit fibroblastic activity, which would prevent localization of the infection (helping its spread to the neighbouring areas) but however, it prevents development of adhesions during healing.

(8) Anti-allergic effect : Glucocorticoids suppress all manifestations of allergy by *preventing release of histamine from the mast cells.*

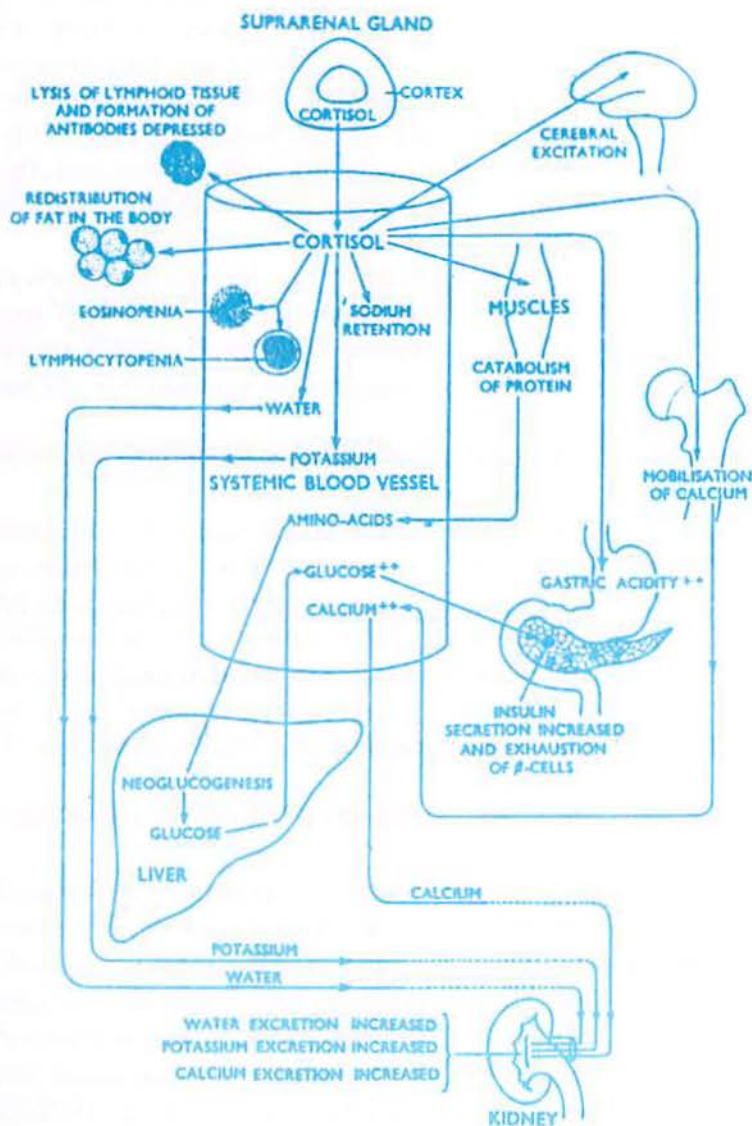


Figure 22 : Functions of glucocorticoids

****** Both 7 and 8 are produced *only by large (pharmacologic) doses of glucocorticoids*. These hormones are also empirically given in other diseases e.g. autoimmune and neoplastic diseases as well as in cases of shock and brain edema. Doses exceeding 20 mg daily given for more than 3 weeks cause persistent inhibition of the hypothalamic-pituitary axis by a negative feed back mechanism, so the secretion of both CRH and ACTH is severely decreased and the adrenal cortex becomes functionless. In such cases, sudden withdrawal of the exogenous hormones leads to signs of adrenocortical insufficiency (*cortisol withdrawal syndrome*). To avoid these effects, the hormones are preferably given in small doses and every other day, and their *withdrawal should be gradual* over several months (= *tapering of glucocorticoid treatment*) because complete recovery of the hypothalamic-pituitary axis and the adrenal cortex requires 2 months up to one year after withdrawal of the hormones.

(9) Effects on other hormones : Glucocorticoids *decrease the secretion of both the growth hormone* (page 20) and *TSH* (page 40).

(10) Effects on the respiratory system : During fetal life, the glucocorticoids *accelerate the formation of surfactant in the lungs*.

Regulation (control) of glucocorticoid secretion

Glucocorticoid secretion is stimulated mainly by the adrenocorticotrophic hormone (**ACTH**) which is secreted by the *corticotrope cells of the anterior pituitary gland*. ACTH is a single-chain polypeptide (containing 39 amino acids) that maintains the structure, size and vascularity of the adrenal cortex. **It stimulates glucocorticoid and androgen secretion** from both *zonae fasciculata and reticularis* (but its effect on zona glomerulosa is minimal) and it also *exerts a considerable MSH activity* (page 14).

Mechanism of action of ACTH and control of its secretion

In the adrenal cortex, ACTH acts by increasing the intracellular *cyclic AMP* content in the target cells. Its secretion is controlled by 2 factors :

- 1. Corticotropin-releasing hormone (CRH) :** This is secreted from the hypothalamus (figure 23) and it promotes ACTH synthesis & release from the corticotropes (by increasing the *cyclic AMP* content in these cells).
- 2. Feedback control :** A negative feedback relation exists between the free plasma glucocorticoid level and the secretion of ACTH. Such effect is produced at both the pituitary and hypothalamic levels (figure 23).

ACTH response to stress

Many stressful stimuli lead to secretion of ACTH (through stimulating CRH secretion from the hypothalamus) e.g. trauma or injury, acute hypoglycemia, anxiety, fear and other emotional stresses. Such stimuli excite many parts of the brain (specially the *limbic system*) which in turn stimulate CRH secretion from the hypothalamus.

Diurnal (circadian) rhythm of ACTH secretion

Normally, ACTH is secreted irregularly throughout the 24 hours and in response, the plasma glucocorticoid level tends to rise and fall. In humans, the *peak of ACTH secretion occurs in the early morning* and is lowest in the evening. This phenomenon is known as the diurnal or circadian rhythm and it is *due to a diurnal variation in CRH secretion*. The *biologic clock* responsible for the diurnal ACTH rhythm is located in the *suprachiasmatic nuclei of the hypothalamus*.

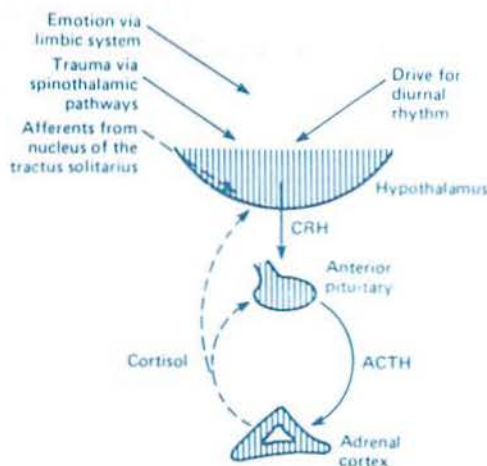


Figure 23 : Control of secretion of glucocorticoids.

Functions (effects or actions) of mineralocorticoids

Mineralocorticoids include mainly *aldosterone* and *deoxycorticosterone (DOC)*. Both are secreted only from the *zona glomerulosa* in almost *equal amounts* but *DOC has only 3 % of aldosterone activity*. They are important for regulating Na^+ and K^+ metabolism and extracellular fluid (ECF) volume. The *normal serum Na^+ level is 135-145 mEq/litre*, while that of K^+ is 3.5-5 mEq/litre.

Mineralocorticoids *increase Na^+ concentration in the ECF* (and consequently the ECF volume) by the following mechanisms :

1. Actions on the kidneys : The kidneys are the major site of action of these hormones, where they act mainly at the *distal convoluted tubules and the collecting ducts, increasing Na^+ reabsorption in exchange with secretion of either K^+ or H^+* (according to the body conditions).

2. Actions outside the kidneys : Mineralocorticoids increase Na^+ absorption from other body fluids than the urine (e.g. *sweat and saliva*) as well as from the *GIT mucosa (specially at the colon)*.

Mechanism of action of aldosterone

Na^+ absorption is promoted by aldosterone through binding to specific *cytoplasmic receptors* in the target cells which increase transcription of *mRNAs resulting in production of certain proteins that alter the cell functions. These proteins increase the activity of Na^+ channels and also stimulate their synthesis* at the luminal borders of the tubular cells. They also *increase the activity of the membrane $\text{Na}^+ - \text{K}^+$ exchangers specially ATPase* (refer to kidney).

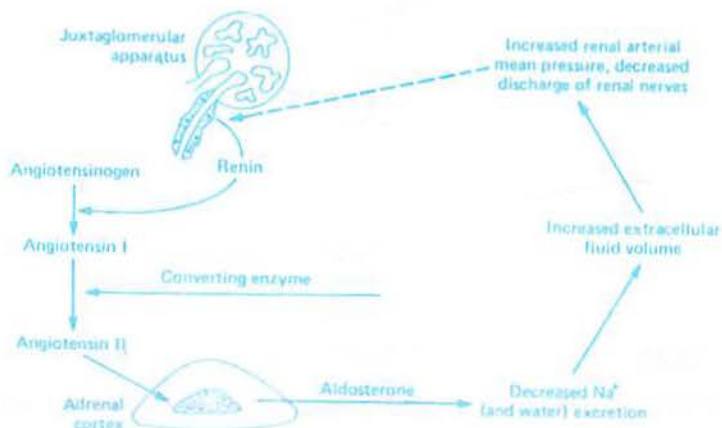


Figure 24 : The feed back mechanism that regulates secretion of renin and aldosterone (the dashed arrow indicates inhibition).

Factors that regulate (control) aldosterone secretion

1. Angiotensin II : *This stimulates conversion of corticosterone to aldosterone in the zona glomerulosa cells and secretion of aldosterone from these cells.* It is formed through the **renin-angiotensin system** which regulates aldosterone secretion by a **feedback mechanism** as follows : A decrease in the ECF volume leads to *renal ischemia* and also increases the sympathetic activity. Both effects stimulate **renin secretion from the juxta-glomerular cells of the kidney** and renin, in turn, leads to formation of **angiotensins I, II & III** (refer to circulation). The latter 2 stimulate aldosterone secretion which causes Na^+ and water retention. This increases the ECF volume, which, in turn, inhibits renin secretion (figure 24).

2. ACTH : This hormone stimulates secretion of mineralocorticoids. However, *aldosterone secretion is reduced within few days* because the resulting hypervolemia inhibits renin secretion which decreases formation of angiotensin II, *but the secretion of deoxycorticosterone (DOC) remains elevated because its secretion is controlled only by ACTH and is not affected by the level of angiotensin II.*

**** A pituitary hormone other than ACTH** helps to maintain the integrity and responsiveness of the zona glomerulosa to angiotensin II. Therefore, immediately after hypophysectomy, both zonae fasciculata and reticularis begin to degenerate but the zona glomerulosa persists for sometime (because it still responds to angiotensin II). However, it degenerates in long standing cases because of absence of this pituitary hormone .

3. Na^+ and K^+ serum levels : Aldosterone secretion varies inversely with serum Na^+ level and directly with serum K^+ level but it is **more sensitive to changes in K^+ than to changes in Na^+** (the Na^+ level must drop about 20 mEq/litre to stimulate aldosterone secretion while such effect can be produced by an increase in K^+ level of only 1 mEq/litre).

4. Other factors :

- (a) The atrial natriuretic peptide (**ANP**) inhibits renin secretion and decreases the responsiveness of the zona glomerulosa cells to angiotensin II.
- (b) The rate of aldosterone secretion shows a **circadian rhythm** being highest in the early morning before awakening and lowest in the evening.
- (c) Aldosterone secretion is increased **together with the glucocorticoids** in **stress conditions**.

**** The high serum K^+ level** directly stimulates the zona glomerulosa cells to secrete aldosterone. On the other hand, the **low serum Na^+ level** stimulates these cells through formation of **angiotensin II**, because it leads to hypovolemia which stimulates renin secretion by the resulting renal ischemia and increased discharge of the renal sympathetic nerves (see next).

**** Renin secretion increases** by renal ischemia or increased discharge in the renal symp. nerves (or both together) in the following conditions :

1. **Hyponatremia** (see above) and **hypotension**.
2. **Constriction of the renal artery or the aorta**.
3. **Drop in the ECF volume i.e. hypovolemia** (e.g. due to hemorrhage or dehydration) or the **intra-arterial vascular volume** (e.g. due to prolonged standing or constriction of the thoracic inferior vena cava).
4. **Some cases of congestive heart failure, nephrosis and liver cirrhosis** (= secondary hyperaldosteronism).
5. **Activation of the sympathetic system** : Sympathetic stimulation and catecholamines increase renin secretion by activating the β_1 adrenergic receptors at the juxtaglomerular cells of the kidneys.

ALDOSTERONE ESCAPE

High doses of aldosterone cause sodium and water retention and increase the ECF volume. However, *after few days this effect disappears* and the **kidneys escape from the effect of aldosterone**, so the excretion of sodium and water increases again although the aldosterone blood level is maintained high. Such phenomenon explains *why only slight edema occurs in hyperaldosteronism*, and it is **due to the increase of the ECF volume itself** which leads to (a) Rise of the arterial B.P., and this leads to **pressure diuresis** (b) Secretion of **ANP**, which causes both natriuresis as well as water diuresis.

THE ADRENAL SEX HORMONES

The adrenal androgens **DHEA and androstenedione** are the main sex hormones secreted by the adrenal cortex. Very small amounts of estrogen and progesterone are also secreted.

Androgens are hormones that produce **masculinizing effects** (i.e. male characteristics) and also promote protein anabolism and growth. Their secretion from the adrenal cortex starts in the young age, **peaks at puberty** then falls to very low values in old age. They are secreted **equally in both sexes** and their plasma levels is the same in both males and females. However, when secreted in normal amounts, they exert **minor effects on reproduction and have very little masculinizing effects** as they exert only 20 % of the activity of testosterone (page 109).

Functions : Androgens help early sexual maturation in males while *in females they cause growth of axillary and pubic hair at puberty*. Their secretion is controlled by *ACTH* and possibly also by a specific *pituitary adrenal androgen-stimulating hormone (but not by the gonadotropic hormones)*.

Disorders (diseases) of the adrenal cortex

[A] Addison's disease (= Adrenocortical hypofunction)

This is **primary adrenal insufficiency (hypocorticism)** i.e. *due to damage of the adrenal cortex itself*. It is usually due to *an autoimmune disease* but, however, some cases are due to destruction of the glands by other diseases specially *tuberculosis and cancer*. **Secondary adrenal insufficiency** due to deficient ACTH secretion and **tertiary adrenal insufficiency** due to deficient CRH secretion may also occur.

Manifestations (symptoms) of Addison's disease

A- Aldosterone deficiency leads to :

1. **Hyponatremia** due to excessive Na^+ loss in the urine. It leads to *hypovolemia and hypotension* due to simultaneous water loss.
2. **Small heart size** because hypotension decreases the heart work
3. **Metabolic acidosis** due to H^+ retention (since H^+ secretion in the kidneys is coupled with Na^+ reabsorption, which is deficient in this disease).
4. **Hyperkalemia** due to deficient K^+ secretion. This causes *muscle weakness, tiredness and characteristic changes in the ECG (refer to CVS)*.

B- Glucocorticoid deficiency leads to :

1. **Hypoglycemia** between meals (fasting leads to fatal hypoglycemia).
2. **Fatigue and general weakness** due to lack of mobilization of substrates that supply energy specially FFAs .
3. **Gastrointestinal symptoms** e.g. anorexia (= loss of appetite), nausea, and vomiting . These effects lead to *loss of weight*.
4. **Liability to water intoxication (in spite of water loss in the urine with Na^+)** : This is due to inability to eliminate excess water loads from the body and is helped by the *plasma hypotonicity* (due to hyponatremia) which favours diffusion of water into the cells.

5. Decreased resistance to stress : Stress conditions aggravate the disease leading to severe collapse and may cause fatal shock (a condition known as *Addisonian crisis*).

6. Certain nervous manifestations (page 52).

7. Dark pigmentation of the skin and mucous membranes e.g. the gum. This is due to *excessive deposition of melanin caused by increased ACTH level in the blood. ACTH exerts a MSH-activity* (page 14) and its secretion is stimulated by a negative feedback mechanism due to reduction of the plasma glucocorticoid concentration. Skin pigmentation particularly occurs at the pressure points, palmar creases, the light exposed areas (e.g. the face and front of the neck), areola of nipples and recent scars.

****** In secondary and tertiary adrenal insufficiency, the symptoms are mild because the *electrolyte metabolism is less affected*. In addition, there is *no pigmentation* because the blood ACTH level is low in these conditions.

****** Patients are advised to take foods rich in Na^+ and poor in K^+ . However, *treatment with both mineralo and gluco-corticoid hormones is essential*.

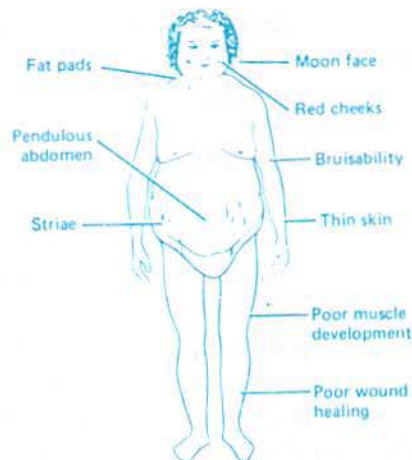


Figure 25 : Typical findings in Cushing's syndrome

[B] Adrenocortical hyperfunction (hypercorticism)

This includes **3 syndromes**, each of which is characterized by overactivity of a particular zone of the gland.

(1) Cushing's syndrome (disease)

This is due to **overactivity of the zona fasciculata** (which leads to excessive secretion of glucocorticoids and to a little extent, also androgens). It occurs as a result of either (a) An adrenocortical tumour (= **Primary hypercorticism or Cushing's syndrome**). This type is *ACTH-independent* and is also produced by prolonged administration of exogenous glucocorticoids (b) Excessive secretion of ACTH by either a pituitary tumour or due to oversecretion of CRH (= **Secondary hypercorticism or Cushing's disease**). This type is *ACTH-dependent* and is also produced by ACTH-secreting tumours in other organs, usually the lungs (= *ectopic ACTH syndrome*). However, it is often difficult to detect the site of these ACTH-secreting tumours.

Manifestations (symptoms) of Cushing's syndrome

(1) **Increased protein catabolism** : This leads to :

- a. Poorly-developed muscles resulting in muscle weakness.
- b. Thin skin and subcutaneous tissues. Wounds heal poorly and minor injuries cause bruises (figure 25).
- c. Bone resorption leading to *osteopenia (or osteoporosis)*. This leads to collapse of the vertebral bodies (and other fractures) resulting in *kyphosis*, which increases the buffalo hump appearance (see below).

(2) **Central (or trunk) obesity** : Body fat is redistributed. Fat collects mainly in the face, abdominal wall, supraclavicular region and upper part of the back (producing a **buffalo hump**), but *not in the limbs which become thin and weak*. As the thin abdominal skin is stretched, the subdermal tissues rupture producing **reddish-purple striae**.

(3) **Hypertension** : This occurs in 85 % of patients as a result of (a) *Hypervolemia* due to increased Na^+ and water retention, which is produced by the excess glucocorticoids and increased secretion of mineralocorticoids and may be also angiotensinogen (b) *V.C. produced by* the glucocorticoids directly and by increasing the vascular reactivity to catecholamines.

Section I- Chapter 4***The adrenal (suprarenal) cortex***

****** There may be significant K^+ depletion, which adds to the state of general weakness.

****** Salt and water retention plus the facial obesity cause a characteristic plethoric and rounded face in this disease that is described as *moon face*.

(4) Impaired glucose tolerance : The increased gluconeogenesis produced by the glucocorticoids leads to hyperglycemia and glucosuria. This together with the decreased peripheral utilization of glucose may produce a type of *secondary diabetes called steroid or adrenal diabetes in the patients who are genetically predisposed to diabetes* (page 94).

(5) Nervous symptoms : The excess glucocorticoids accelerate the basic EEG rhythms and produce *mental abnormalities* (e.g. irritability, anxiety, insomnia, emotional disturbances, depression and toxic psychoses) which are more severe than those occurring in Addison's disease (page 52).

(6) Androgenic manifestations : These appear in females due to more secretion of the *adrenal androgens* (e.g. *hirsutism and acne*).

(7) Blood changes : *Mild polycythemia and lymphopenia* often occur.

(8) Increased susceptibility to infections as a result of *depression of the immune system* (due to lymphopenia).

****** In cases that are ACTH-dependent i.e. Cushing's disease or secondary hypercorticism (see above), there is also *skin pigmentation and more secretion of the mineralocorticoid deoxycorticosterone and the adrenal androgens*. It is to be noted that ACTH secretion is decreased in primary hypercorticism (i.e. Cushing's syndrome) by negative feedback.

****** The disease can be promptly treated by surgical removal of the tumours whether in the adrenal cortex or in the adenohypophysis. Drugs that inhibit cortisol secretion or functions can also be used, but surgery is the basic treatment. It was noticed that following removal of an adrenocortical tumour, many patients develop a syndrome called **Nelson's syndrome**. This is characterized by *hyperpigmentation of the skin and signs of increased intracranial tension* that occur due to development of rapidly growing ACTH-secreting tumours (which may be malignant) in the adenohypophysis.

(II) The adrenogenital syndrome

This is due to excessive secretion of **adrenal androgens**. In adults, it is often due to tumours in the **zona reticularis**, but in children, it is usually due to exposure of the fetus to excess androgens during the period *between the 8th and 13th weeks of pregnancy*. This can be produced by androgens transmitted from the mother but more commonly, it is the result of **congenital adrenal hyperplasia** which occurs due to congenital deficiency of certain enzymes specially the **11 and 21 beta hydroxylase enzymes**. In this condition, glucocorticoid synthesis is inhibited, and the metabolic pathways in the adrenal cortex are shunted to the production of excess androgens. The low plasma glucocorticoid level stimulates release of ACTH by negative feedback which causes adrenal hyperplasia and further increases the synthesis and secretion of androgens.

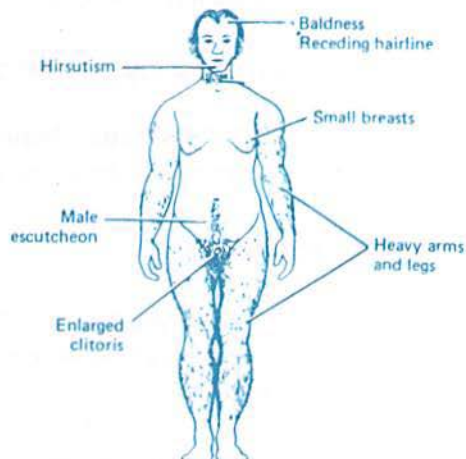


Figure 26 : The adrenogenital syndrome (virilism) in an adult woman.

Manifestations (symptoms)

(A) In females

Adult females show signs of masculinization (= Virilism or Virilization). On the other hand, if the disease occurs in a female fetus, it causes *female pseudohermaphroditism* (i.e. the patient is born with the genetic constitution and gonads of females but with the external genitalia of males) and signs of **virilism** develop later in life.

VIRILISM : This is development of male secondary sex characteristics in females. The size of skeletal muscles increases together with *hirsutism, bitemporal recession of the frontal scalp hairline and may be baldness, appearance of beard and moustache* (figure 26), *deep coarse voice* (due to laryngeal growth), *male escutcheon* (hair growth in the midline between the umbilicus and pubic area) and suppression of the effects of estrogen (resulting in *amenorrhea and infertility, atrophy of the breasts and external genitalia except the clitoris which is enlarged*).

(B) In males

A male fetus having excessive secretion of **adrenal androgens** is born normal, but he will show **precocious pseudopuberty** i.e. early development of secondary sex characteristics without testicular growth. However, if the excess androgen secretion occurs during adult life, only the already existing male characteristics will be intensified, and since there is no complaint by the patient, the condition usually passes unnoticed.

(III) Conn's syndrome (primary hyperaldosteronism)

This is due to overactivity of the **zona glomerulosa** as a result of tumours, which leads to excessive secretion of the mineralocorticoids.

Manifestations (symptoms)

1. Na^+ retention : This is associated with equivalent water retention, so there will be *no hypernatremia*. It results in *expansion of the ECF volume, hypervolemia and hypertension*. However, these effects are *moderate and no (or slight) edema occurs* because of the phenomenon of **aldosterone escape** (page 58). *Metabolic alkalosis* may develop due to excess H^+ secretion in the renal tubules in exchange with the increased Na^+ reabsorption.

2. **K⁺ depletion** : This leads to *hypokalemia*, which leads to severe muscle weakness, renal damage (= *hypokalemic nephropathy*) as well as many cardiac effects (refer to CVS).

****** Treatment of Conn's syndrome can be achieved by surgical removal of the causing tumour and administration of aldosterone antagonistic drugs.

THE ADRENOCORTICAL FUNCTION TESTS

(1) *Measurement of the serum levels of Na⁺ and K⁺, cortisol, DHEA, aldosterone and ACTH as well as the plasma pH* give good indication about the functions of the adrenal cortex and nature of its disorders.

(2) *Determination of the steroid metabolites in urine* : The commonly measured metabolite is the *17-ketosteroids*, which increase in Cushing's disease and the adrenogenital syndrome, and decrease in Addison's disease.

(3) *ACTH test* : A test dose of ACTH is injected i.v. and the plasma cortisol level is measured after one hour. It increases in normal subjects and in cases of secondary and tertiary adrenocortical insufficiency but not in the primary type (so this test can be used to differentiate between the primary and the other causes of adrenal insufficiency).

(4) *Saline suppression test* : An isotonic saline solution is given i.v. for 4 hours at a rate of 400 ml / hour then the plasma level of aldosterone is measured. It decreases in normal subjects but is not affected in Conn's syndrome (so it is helpful in the diagnosis of this disease).

(5) *Salt deprivation test* : A salt-free diet is given for 3 days then the NaCl content in the urine is measured. Normally, the urinary NaCl content should be markedly decreased (and may be absent), but in adrenocortical insufficiency the urinary NaCl excretion is not affected.

CHAPTER 5

THE ADRENAL (SUPRARENAL) MEDULLA

The 2 adrenal (or suprarenal) medullae secrete **3 catecholamines** [*adrenaline (or epinephrine), noradrenaline (or norepinephrine) and dopamine*]. In addition, they also secrete small amounts of *opioid peptides* (specially met-enkephalin) and *adrenomedullin* (a vasodepressor polypeptide), the functions of which are unknown.

Histological structure and innervation

The adrenal medullae are *modified sympathetic ganglia* in which the postganglionic neurons become secretory cells, and *glucocorticoids are necessary for their normal development*. The secretory cells are called *chromaffin cells* and they are **2 types** : 90 % *epinephrine-secreting cells* and 10 % *norepinephrine-secreting cells* (the cells that secrete dopamine are unknown), and they are innervated by *sympathetic cholinergic preganglionic neurons from the greater splanchnic nerves*.

Catecholamines' concentrations in the plasma

Normally, about 80 % of the catecholamines output from the adrenal medullae is epinephrine while *only 20 % is norepinephrine*. (however, the latter is also added to the blood from the noradrenergic sympathetic nerves). About 70 % of these hormones are conjugated in the blood to sulphate. The **normal free plasma norepinephrine level is about 300 pg/ml**, while that of **epinephrine is about 30 pg/ml** (pg = picogram). 1/2 of the plasma dopamine comes from the adrenal medullae while the other 1/2 comes from the sympathetic ganglia and other components of the autonomic nervous system (and its free plasma level is about **35 pg/ml**).

Mechanism of action of catecholamines

The effects of catecholamines are produced through acting on 5 types of receptors in the effector organs : The **alpha 1 & 2 and beta 1, 2 & 3 receptors**. At all beta receptors, the hormones act by *increasing* the intracellular cyclic-AMP content. On the other hand, at the alpha₁ receptors, the hormones act by *increasing* DAG and IP₃ (which increases the intracellular Ca²⁺ content) while at the alpha₂ receptors, they act by *decreasing* the intracellular cyclic-AMP content (pages 8 and 9).

Effects (actions) of catecholamines

The adrenal medullae operate with the sympathetic nervous system as one system (= *sympathoadrenal system*). This system acts *during emergencies* to prepare the individual for **fight or flight** when threatened. This was called by Cannon "*the emergency function of the sympathoadrenal system*", and it is produced through exerting widespread effects on almost all systems of the body as follows :

1. The cardiovascular system

Catecholamines directly increase the heart rate and myocardial contractility. However, **norepinephrine also produces V.C. in most organs**, and this causes marked increase in both the systolic and diastolic B.P. Accordingly, the arterial baroreceptors are stimulated thus leading to *reflex bradycardia*, which overcomes the direct effect of the hormone on the heart, resulting in *decrease of the cardiac output*.

On the other hand, **epinephrine produces V.D. in the skeletal muscles** which overcomes its V.C. effect elsewhere. This decreases the peripheral resistance (so the diastolic B.P. is not changed or it may slightly decrease). At the same time, the systolic B.P. is increased (as a result of the direct effect of the hormone on the heart) and accordingly, *the pulse pressure is increased*. However, the mean arterial B.P. increases only slightly and the baroreceptor mechanism does not produce bradycardia, thus *under the effect of epinephrine, the cardiac output is increased*.

2. Skeletal muscles

Catecholamines (particularly epinephrine) strengthen skeletal muscle contraction and delay the onset of its fatigue because they (a) Stimulate glycogenolysis and lipolysis (which supply glucose and free fatty acids i.e. more energy) (b) Produce local V.D. in the muscles (which provides more blood supply).

3. Nervous system

Catecholamines excite the nervous system, and increase the mental activity and alertness through stimulating the **reticular activating system**.

4. Respiration

Catecholamines increase the rate and depth of respiration by (a) Direct excitation of the respiratory centre as a part of their excitatory effect on the nervous system (b) Increasing the metabolic rate.

5. Blood glucose level

Catecholamines (specially epinephrine) **stimulate glycogenolysis in the liver**, resulting in *hyperglycemia* (which may lead to *glucosuria*).

6. Metabolic rate (calorigenic action)

Catecholamines increase the metabolic rate and O_2 consumption (thus increasing heat production). The initial rise in the metabolic rate is *liver-independent* and may be due to either (a) The cutaneous V.C. effect (which decreases heat loss, leading to rise of the body temperature) or (b) The increase in muscular activity. However, the delayed rise is due to oxidation of lactate in the liver (since it is abolished after hepatectomy).

7. Adipose tissue

Catecholamines mobilize free fatty acids (FFAs) from adipose tissue which leads to **increase of the plasma FFAs level**.

8. Smooth muscles

The effects of catecholamines on smooth muscles are **similar to those produced by sympathetic stimulation** (refer to autonomic N.S.).

9. Kidneys

Catecholamines cause **oliguria** (= decreased urine volume) due to V.C. of the renal blood vessels. Such effect is beneficial in certain emergencies e.g. the hypovolemic shock caused by severe hemorrhage.

10. Blood

Catecholamines cause **contraction of the splenic capsule** which adds about 200 ml blood to the general circulation (thus increasing the blood volume, red cell count, Hb content and hematocrit value). They also **shorten the clotting time** because they stimulate synthesis of fibrinogen and prothrombin and increase the activity of clotting factor 5.

11. Electrolytes

Catecholamines cause an initial rise in the plasma K^+ level (due to K^+ release from the liver) followed by its fall (due to K^+ entry into the skeletal muscles). Therefore, catecholamines may play a role in **regulating the ratio between the extracellular and intracellular K^+** .

12. Vision

Catecholamines **increase the visual fields** by producing pupillo-dilatation, exophthalmos and widening of the palpebral fissure.

Role of catecholamines in various emergencies

Catecholamines are essential for an efficient body performance during various emergencies as shown in the following conditions :

1. Muscular exercise : They help skeletal muscles to *perform extrawork* through increasing (a) Their blood supply (by increasing the cardiac output and causing local V.D. in the muscles) (b) The energy supply (glucose and fatty acids) (c) The blood oxygen content, by increasing both the blood volume (due to splenic contraction) and pulmonary ventilation (by producing bronchodilatation).

2. Hemorrhage : They *prevent development of hypovolemic shock* through producing (a) V.C. in the cutaneous and splanchnic vessels (b) Heart acceleration (c) Increase of the blood volume (d) Bronchodilatation (which aids better ventilation) (e) Shortening of the clotting time (which helps hemostasis).

3. Hypoglycemia : They increase the blood glucose level through stimulating the process of *glycogenolysis in the liver*.

4. Exposure to cold : They help to maintain a constant body temperature through *preventing heat loss* (by causing V.C. in the cutaneous blood vessels) and *increasing the heat production* (by their calorogenic action).

****** When the adrenal medullary secretion is increased, *the ratio of norepinephrine to epinephrine is generally unchanged*.

Accordingly, there is *no selective secretion of catecholamines according to the nature of emergency* as shown e.g. in case of hemorrhage, in which epinephrine is still predominantly secreted although norepinephrine is more useful because of its potent V.C. effect.

However, it was found that *more norepinephrine is secreted in emotional stresses with which the individual is familiar, whereas more epinephrine is secreted in cases in which the individual does not know what to expect*.

Effects of dopamine

The physiologic functions of the circulating dopamine are *unknown*. However, an injected dose of dopamine **produces V.C.** (probably by releasing norepinephrine) except in the mesentery and kidneys where it produces V.D. (probably by acting on certain specific dopaminergic receptors). Dopamine also exerts

a +ve *inotropic effect on the heart* so the net effect is *an increase in the systolic blood pressure and no change in the diastolic blood pressure*. Because of these actions, dopamine can be used in the *treatment of traumatic and cardiogenic shock*. Dopamine also causes *natriuresis* probably by inhibiting the renal $\text{Na}^+ - \text{K}^+$ ATPase.

Secretion of the SUPRARENAL MEDULLA is under control of the SYMPATHETIC NERVOUS SYSTEM

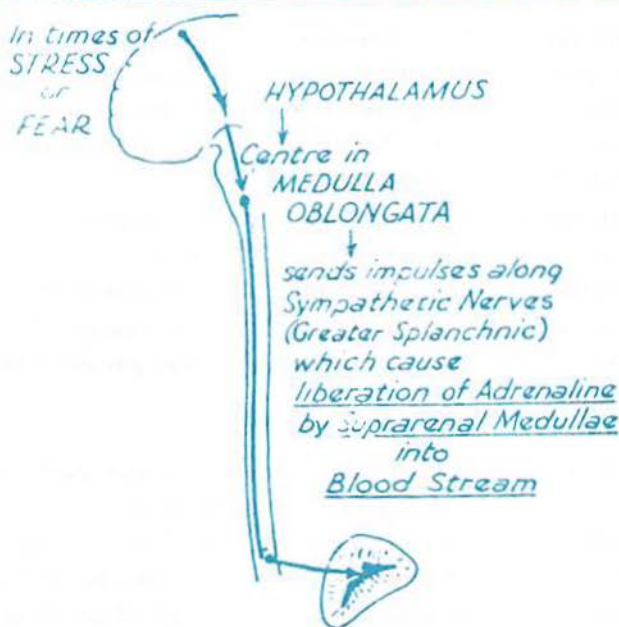


Figure 27 : Regulation (control) of adrenomedullary secretion.

Regulation (control) of adrenomedullary secretion

The secretion of catecholamines from the adrenal medullae is little during rest and is further decreased during sleep. It is controlled by its sympathetic supply and it markedly increases in cases of *emergency and during the alarm response* as a part of the diffuse sympathetic activity in these conditions (in order to amplify and prolong the sympathetic effects). The vasoconstrictor centre (V.C.C.) in the medulla oblongata is connected to the origin of the greater splanchnic nerve via the **reticulospinal tract**

(figure 27). When this centre is stimulated, the neural discharge to the adrenal medullae increases leading to an increase in catecholamines secretion and vice versa. The activity of this centre is affected by impulses discharged from the following sites :

1. The hypothalamus : This is stimulated in various emergency conditions (e.g. hypoglycemia, exposure to cold, stress and emotions), and subsequently it sends *stimulatory signals to the V.C.C.* which leads to an increase in the secretion of catecholamines.

2. Arterial baroreceptors (in the carotid sinus & aortic arch) : When these receptors are stimulated (by a rise of the arterial B.P.), they send inhibitory signals to the V.C.C. which leads to a decrease in the secretion of catecholamines, and vice versa (refer to circulation).

3. Peripheral chemoreceptors (in the carotid and aortic bodies) : When these receptors are stimulated (e.g. in cases of hypoxia and asphyxia), they send stimulatory signals to the V.C.C. which leads to an increase in the secretion of catecholamines.

4. Volume receptors in the right atrium : When these receptors are stimulated (by an increase in the central venous pressure), they send inhibitory signals to the V.C.C. which leads to a decrease in the secretion of catecholamines, and vice versa.

Mechanism of release (secretion) of catecholamines

The sympathetic signals to the gland lead to release of *acetylcholine* at the preganglionic nerve endings, which causes opening of Ca^{2+} channels in the membranes of the secreting cells (so Ca^{2+} diffuse from the ECF into these cells). In the secretory cells, the hormones are stored in granules bound to *ATP* and a protein called *chromogranin A*, and Ca^{2+} lead to extrusion of the secretory granules by *exocytosis* so that the hormones, ATP and chromogranin A are all released together into the bloodstream.

Pheochromocytoma

This is a *tumour of the adrenal medulla*. Its main symptom is *sustained hypertension* because most tumours secrete excess *norepinephrine only or together with little epinephrine*. However, *some tumours secrete epinephrine only*, and in 15 % of these cases, the hormone is secreted *episodically* producing intermittent bouts of severe *systolic hypertension, palpitations and headache as well as glucosuria*.

CHAPTER 6

THE PARATHYROID GLANDS AND CALCIUM METABOLISM

In humans, there are usually 4 parathyroid glands that are embedded in the posterior surface of the thyroid gland (figure 28). They secrete a *polypeptide hormone* (containing 84 amino acids) called the *parathyroid hormone or parathormone (PTH)*. The primary function of this hormone is *regulation of the Ca^{2+} concentration* in the extracellular fluid, and for this reason **it is essential to life** (page 2).

The normal plasma level of PTH is *10-55 pg/ml* and it is inactivated mainly in the liver by the Kupfer cells and to a lesser extent in the kidneys.

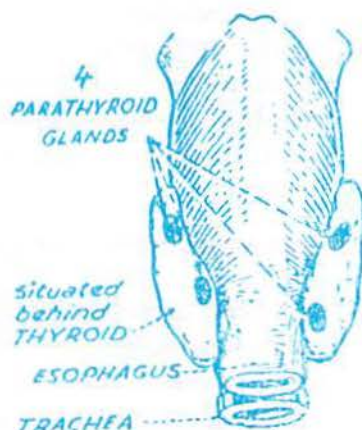


Figure 28 : The human parathyroid glands.

ACTIONS OF THE PARATHORMONE

The parathormone (PTH) is a major regulating factor for *both calcium (Ca^{2+}) and inorganic phosphate (PO_4^{3-}) concentrations in the body fluids*. Normally, the **plasma PO_4^{3-} concentration is inversely related to the Ca^{2+} concentration**, so the *product of $\text{Ca}^{2+} \times \text{PO}_4^{3-}$ is always constant* (which is known as the solubility product). The *main function of PTH is to increase the plasma Ca^{2+} level and decrease the plasma PO_4^{3-} level* (so as to maintain the solubility product constant).

PARATHORMONE acts on **KIDNEY TUBULES**, **BONE** and on **GUT** to maintain **BLOOD CALCIUM** level at 11mg/100ml PLASMA

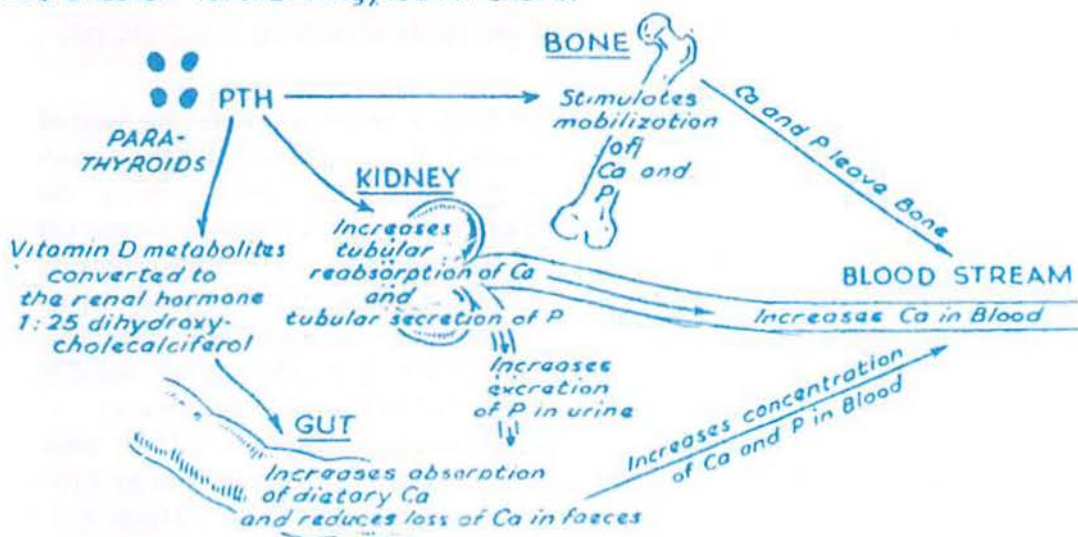


Figure 29 : Actions of the parathormone.

(A) Mechanisms of increasing the plasma Ca^{2+} level

The PTH increases the plasma Ca^{2+} level by 3 mechanisms (figure 29) :

1. **Increasing Ca^{2+} mobilization from bones :** PTH acts directly on bone increasing the formation and activity of the *osteoclasts* (= bone eating cells) which destroy the bone by releasing H^+ and protease enzymes, resulting in bone resorption and Ca^{2+} mobilization to the bloodstream.
2. **Increasing Ca^{2+} reabsorption in the distal convoluted tubules of the kidneys.**
3. **Increasing absorption of Ca^{2+} from the intestine** indirectly through increasing formation and activity of 1, 25 - Dihydroxycholecalciferol (= DHCC or calcitriol), which is the active metabolite of vitamin D_3 (page 81).

(B) Mechanism of decreasing the plasma PO_4^{3-} level

The PTH decreases the PO_4^{3-} plasma level by exerting a *phosphaturic action* (i.e. increasing PO_4^{3-} excretion in the urine) through *inhibiting PO_4^{3-} reabsorption in the proximal convoluted tubules of the kidneys*.

Mechanism of action of the parathormone

The PTH acts mainly through activating the adenylyl cyclase enzyme and increasing the *cyclic AMP content* in the target cells (page 8).

Regulation (control) of parathormone secretion

The main regulating factor for PTH secretion is the **plasma ionized calcium (Ca^{2+}) level** which directly controls the parathyroid glands by a *negative feedback mechanism*. When the plasma Ca^{2+} level is high, the secretion of the hormone is inhibited and calcium is deposited in bones. On the other hand, when the plasma Ca^{2+} is low, the secretion of the hormone is increased and calcium is mobilized from bones. Mg^{2+} generally exerts similar effects as Ca^{2+} . In addition, *Mg^{2+} is required to maintain normal parathyroid secretory responses*, and this explains why hypocalcemia may occur in Mg^{2+} deficiency. PTH secretion is also affected by the following factors :

1. **Calcitriol** : Its increase inhibits PTH secretion (page 83) and vice versa
2. **Plasma PO_4^{3-} level** : Its increase stimulates PTH secretion by lowering the plasma Ca^{2+} level and inhibiting formation of calcitriol (page 82).
3. **Nervous factors** : PTH is increased by beta-receptor stimulating drugs.

HYPOPARATHYROIDISM

In man, hypoparathyroidism occurs when at least 3 parathyroid glands are damaged. This may occur as a result of **autoimmunity or accidentally during thyroid surgery**. It leads to **hypocalcemia** i.e. reduction of the plasma Ca^{2+} level (normal value 9 - 11 mg %) and **hyperphosphatemia** i.e. increase of the plasma PO_4^{3-} level (normal value 2.5 - 4.5 mg %).

*** **Pseudohypoparathyroidism** : Signs of the disease may occur with normal or elevated plasma levels of PTH. These cases are called *pseudo-hypoparathyroidism* and are due to unresponsiveness of the tissues to the hormone as a result of congenital receptor disorders.

Hypocalcemia occurs as a result of depression of the osteoclastic activity and bone resorption as well as decreased formation of 1,25-DHCC and reabsorption of Ca^{2+} in the distal tubules of the kidneys. It causes numbness and tingling sensations, muscle weakness, cardiac arrhythmias and GIT disorders. It also *increases the excitability of the nervous system and the neuromuscular junctions leading to **tetany***, which is the *main characteristic feature of hypoparathyroidism*.

Definition of tetany

Tetany is a state of **spastic contraction of the skeletal muscles due to an increase in the neuromuscular excitability** that occurs as a result of a **decrease in the ionized plasma Ca^{2+} level**.

Causes of tetany

The causes of tetany are *those that cause hypocalcemia*, the most important of which include the following :

- (1) Hypoparathyroidism (see above).
- (2) Renal failure (due to decreased formation of 1,25-DHCC as well as calcium reabsorption in the distal convoluted tubules).
- (3) Alkalemia (which promotes precipitation of calcium phosphate, so the plasma ionized Ca^{2+} level is decreased).
- (4) Vitamin D deficiency (decreases Ca^{2+} absorption from the intestine).
- (5) Low calcium content in the diet, or diets that combine with calcium and form unabsorbable calcium compounds.
- (6) Steatorrhea (= fatty diarrhea), which decreases calcium absorption.

Types and manifestations (symptoms) of tetany

Depending on the plasma Ca^{2+} level, there are **2 main types of tetany** :

(A) Manifest tetany

This occurs when the *plasma Ca^{2+} level drops below 7 mg %*. There is stiffness of the skeletal muscles interrupted by attacks of spasmodic contractions caused by spontaneous discharge of action potentials at the motor end plates. In the hands and feet, a characteristic pattern of spasm known as *carpopedal spasm* may occur. In the carpal spasm (figure 30), the hands adopt the *obstetric position* (= *accoucheur hand*), in which the wrist and metacarpophalangeal joints are flexed while the interphalangeal joints are extended and the thumb is adducted into the palm. In the pedal spasm, the feet and toes are plantar flexed (but the ankle joints may be dorsiflexed). In severe conditions, generalized convulsions may occur.

Spasmodic contraction of the laryngeal muscles leads to respiratory distress and cyanosis, and if severe or prolonged, the glottis may be completely closed leading to death as a result of asphyxia (a condition called *laryngeal stridor*).

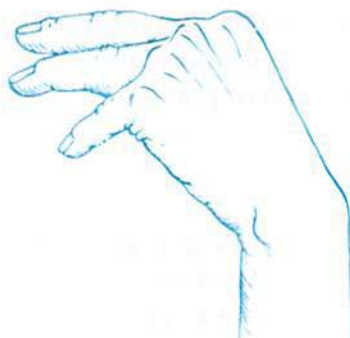


Figure 30 : The obstetric hand (= accoucheur hand) seen in manifest tetany.

(B) Latent tetany

This occurs when the *drop in the plasma Ca^{2+} level does not reach 7 mg %*. Tetany appears only in conditions that increase the neuromuscular excitability e.g. emotions, hyperventilation (due to the tendency to develop alkalosis), pregnancy and lactation. It can be diagnosed *by measuring the ionized plasma Ca^{2+} level* or by the following tests (= **provocation tests**) :

(1) **Trousseau's test** : The cuff of a sphygmomanometer is wrapped around the arm and the pressure is raised above the systolic B.P. for 3 minutes (to occlude the circulation). In case of latent tetany, carpal spasm appears because the effects of hypocalcemia are potentiated by ischemia.

(2) **Chvostek's test** : Tapping over the facial nerve (*by a hammer*) in front of the ear (at the angle of the jaw) causes quick contractions of the ipsilateral facial muscles specially those of the upper lip.

(3) **Erb's test** : Stimulation of a superficial motor nerve by a weak Galvanic current which normally produces no effect, causes a prolonged spasmodic contraction of the muscles supplied by the stimulated nerve.

Treatment of tetany

1. Intravenous injection of a soluble calcium salt (e.g. calcium gluconate or chloride) *during the acute attacks*.
2. Giving diets rich in calcium and vitamin D (and vitamin D by injection).
3. **Dihydrotachysterol (= A. T. 10)** : This is a synthetic steroid which produces similar effects as PTH. However, it is preferred because no antibodies are formed against it (the *natural PTH is not used because it leads to formation of antihormones, and in addition, it acts for a shorter duration and is much more expensive*).

HYPERPARATHYROIDISM

This condition occurs primarily as a result of parathyroid tumours, and is associated with **excessive bone resorption** that leave multiple cysts in the bones (so the condition is also called *osteitis fibrosa cystica*). Accordingly, bones become weak and liable to *spontaneous fractures* (which may be the presenting symptom). The excessive Ca^{2+} mobilization to the bloodstream leads to **hypercalcemia** which causes the following

1. Depression of the neuromuscular excitability which causes *muscle weakness, decrease of the muscle tone* (= flaccidity) and *constipation*.

2. **Hypercalcuria** in spite of the increased Ca^{2+} reabsorption by the effect of PTH (because of the excessive Ca^{2+} filtration in the renal glomeruli). This leads to (a) **Polyuria and polydipsia** (b) **Recurrent formation of renal stones** (which may also be the presenting symptom) (c) **Nephrocalcinosis** that may terminate by *renal failure*.

3. In severe cases, **metastatic calcification** may occur in other tissues e.g. the cornea, lungs and arterial walls (= **parathyroid poisoning**).

4. **Cardiac arrhythmias**.

*** **Secondary hyperparathyroidism** : In cases associated with chronic decrease of the plasma Ca^{2+} level (e.g. rickets and chronic renal disease) there is feedback stimulation of the parathyroid glands resulting in *compensatory parathyroid hypertrophy* which is known as secondary hyperparathyroidism.

The parathyroid hormone related protein (PTHrP)

A protein with PTH activity is produced by many tissues e.g. the breasts (and is discharged with milk), smooth muscle, brain and teeth (where it is important for *teeth eruption*). It is formed of 140 amino acids, and is called **parathyroid hormone related protein (PTHrP)**. It is a tissue factor that acts where it is produced. It stimulates *growth of cartilage* in the fetus and is also involved in Ca^{2+} transport in the placenta.

** *Hypercalcemia is commonly present in cancer patients*. About 80 % of these patients have elevated blood levels of **PTHrP** secreted by the tumour (specially cancers of the breast, kidney, ovary and skin). In the remaining 20 % of cases, the hypercalcemia is due to erosion of bones by metastases of the tumour, probably by **certain prostaglandins (such as PGE)** that are released from the tumour cells.

CALCIUM METABOLISM

Calcium is an *essential element* and its chief sources are milk, cheese, eggs and green vegetables. It is absorbed in the small intestine mainly by an active process, and its absorption is stimulated by 1,25-DHCC (= calcitriol, page 81) and *undergoes adaptation* (i.e. it is increased when the calcium intake is low and decreased when the calcium intake is high) also secondary to changes in 1,25-DHCC plasma level (page 82). Calcium performs the following functions :

1. It maintains the normal *excitability of nerves and muscles*.
2. It is important in *neuromuscular transmission*.
3. It is essential for *muscle contraction*.
4. It is a second messenger in many hormonal actions (page 8).
5. It maintains normal permeability of *cell membranes and capillaries*.
6. It is essential for *activation of many enzymes*.
7. It is essential for the *formation of normal bones and teeth*.
8. It is essential for *blood coagulation*.
9. *It is essential for the release of most neurotransmitters*.

CALCIUM HOMEOSTASIS AND TURNOVER

In normal adult individuals, *the daily calcium requirement is about 600 mg*. However, the intestine receives about *1500 mg of calcium daily* (1000 mg from diet and 500 mg from the digestive juices), 900 mg of which are lost in the feces and 600 mg are absorbed, with a **net gain of 100 mg**. These enter the *calcium pool* in the plasma and ECF which is in a continuous turnover (i.e. constantly exchanging) in (a) The intestine (where calcium is secreted then reabsorbed) (b) The kidneys (where calcium is filtered then reabsorbed) (c) The intracellular fluid (d) The bones.

Normal calcium balance is maintained largely by calcium excretion in the *feces and urine*. Fecal excretion is about 900 mg daily (see above). On the other hand, the *kidneys filter about 10 gm calcium daily*, of which 99 % is reabsorbed while 1 % (100 mg) is excreted in the urine. In this way, the **daily calcium intake and output are equal** (about 1000 mg each) .

CALCIUM CONTENT AND DISTRIBUTION IN THE BODY

The adult human body contains about **1100 gm of calcium**, 99 % of which is present in the bones (skeleton) while the remaining part is present in the intracellular and extracellular fluids.

Calcium in the plasma

The normal plasma calcium level averages **10 mg %** (range 9-11 mg %). It is present in the following forms :

(1) Nondiffusible (bound to albumin and globulin, specially albumin).

This is about 4.5 mg % and is **biologically inactive**.

(2) Diffusible : This is about 5.5 mg % and is **2 types** :

a. Non-ionized (forming complexes with bicarbonate and citrate). It is about 0.5 mg %.

b. Ionized (Ca^{2+}) : This is about 5 mg %. It is the **biologically active fraction** that is necessary for most of the functions of calcium and therefore, it is under strict control to be maintained constant.

****** Most methods used for estimating the plasma calcium level measure the *total plasma calcium level* and not the biologically active ionized plasma Ca^{2+} level, because measurement of the latter alone is difficult (but it can still be done by use of a calcium-sensitive electrode). These methods would give false evaluation of the plasma Ca^{2+} level because the amount of calcium bound to the plasma proteins varies proportionately with the level of these proteins. Since calcium is bound mostly to albumin, it is necessary when evaluating the plasma Ca^{2+} level to *measure the plasma albumin level also then correcting the result according to this level*.

Calcium in the bones

Bones contain about **1000 gm of calcium**, which is **2 types** :

1. 99.5 % is present as **stable salts** that are *very slowly exchangeable with the plasma calcium*.

2. 0.5 % (about 5 gm) is **readily exchangeable**. It constitutes a reservoir that is in equilibrium with the plasma calcium and keeps it constant at **7 mg %** in absence of the PTH (*the main regulator of calcium homeostasis*).

PHOSPHORUS

This is an important constituent in many vital substances e.g. ATP, cAMP, 2,3-DPG and others. In addition, protein phosphorylation is essential for hormonal action (chapter 1). The body contains **500-800 gm** most of which is in the bones, mainly as hydroxyapatites. The total plasma phosphorus is about **12 mg %**, one third of which (average 4 mg %) is in the inorganic forms : PO_4^{3-} , HPO_4^{2-} and H_2PO_4^- .

Inorganic phosphate is absorbed in the duodenum and small intestine and like calcium is *stimulated by 1,25 DHCC* (but unlike calcium, it undergoes *no adaptation*). It is filtered in the renal glomeruli then reabsorbed in the proximal convoluted tubules (*but this is powerfully inhibited by the PTH*).

HORMONAL CONTROL OF CALCIUM METABOLISM

3 main hormones affect calcium metabolism. These hormones may be called **calcitropic hormones**, and include **PTH, calcitonin and vitamin D**. In addition, certain other hormones also play a role. PTH has already been discussed and the role of the other hormones is discussed below.

CALCITONIN

This is a **calcium-lowering polypeptide hormone** (containing 32 amino acids) that is secreted by the **parafollicular cells of the thyroid gland** (so it is also called **thyrocalcitonin**). It was also found in certain other tissues (so total thyroidectomy does not reduce the calcitonin circulating level to zero). The actions of calcitonin are mediated by stimulating the adenylyl cyclase enzyme and increasing the intracellular content of **cyclic AMP** (page 8).

Regulation (control) of calcitonin secretion

Calcitonin secretion is regulated by the following factors :

1. **Plasma Ca^{2+} level** : Calcitonin is secreted when the plasma Ca^{2+} level exceeds 9.5 mg %.
2. **Gastrointestinal hormones** : Several GIT hormones (e.g. gastrin, secretin, and CCK) stimulate secretion of calcitonin.
3. Calcitonin secretion is also stimulated by dopamine, beta adrenergic stimulating drugs and estrogens.

Actions of calcitonin

Calcitonin decreases the plasma Ca^{2+} level through acting on the bones and kidneys where it exerts the following effects :

1. **Bones** : Calcitonin ***inhibits bone resorption*** by *reducing the activity of the osteoclasts* (thus it helps Ca^{2+} deposition in bones).
2. **Kidneys** : Calcitonin increases the urinary excretion of Ca^{2+} by *inhibiting its reabsorption from the renal tubules*.

Importance of calcitonin

1. Its release following meals (by the gastrin hormone) helps *prevention of postprandial hypercalcemia*.
2. Its plasma level *increases during pregnancy and in lactating women*. This protects the mother's bones from excessive loss of calcium.
3. Its plasma level *is more in children than in adults*, which helps bone growth and development of the skeleton.
4. It is used in the treatment of a serious bone disease called **Paget's disease** which is characterized by excessive osteoclastic activity.

VITAMIN D

The term "vitamin D" refers to a group of sterols that are formed by the action of ultraviolet rays on certain provitamins. **Vitamin D₃ (= cholecalciferol)** is important in man because its provitamin is **7-dehydrocholesterol**, and this is present in the skin of man (so vitamin D₃ is sometimes called **the skin hormone**). Vitamin D₃ is one of the **fat-soluble vitamins** that is also naturally present in certain foods specially fish liver oils.

Whether ingested in diet or formed in the skin by the action of sunlight on 7-dehydrocholesterol, **vitamin D₃ is not active by itself**. It is transported in the plasma bound to a specific globulin called *vitamin D binding protein (DBP)* and is **activated as follows** (figure 31) :

(1) In the **liver**, vitamin D₃ is converted by activity of the 25-hydroxylase enzyme to **another inactive metabolite** called 25-hydroxycholecalciferol (= **25-HCC or calcidiol**).

(2) In the **proximal convoluted tubules of the kidneys**, calcidiol is converted by activity of the *1 alpha hydroxylase enzyme* to the **active metabolite** 1,25-dihydroxycholecalciferol (= **1,25-DHCC or calcitriol**) and the latter enters the blood (in which the calcitriol level is about 0.03 ngm/ml). Since calcitriol is transported by the bloodstream from the kidneys to distant target organs (the intestine, bone and teeth), it is **considered to be a steroid hormone** (and similar to these hormones, it also acts on intracellular receptors that induce transcription of mRNA).

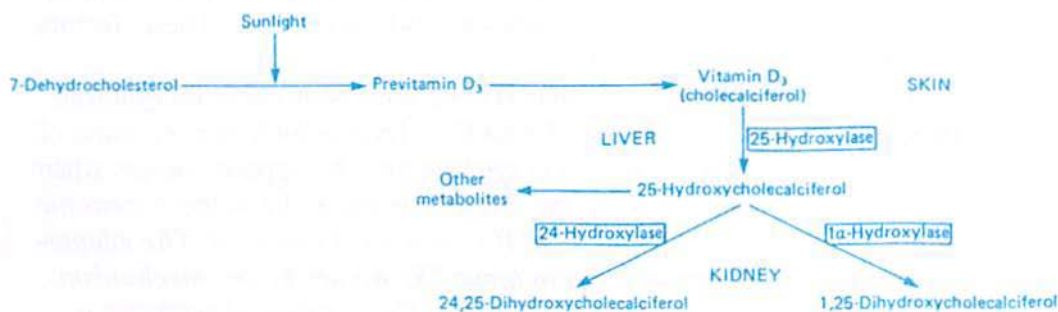


Figure 31 : Activation of vitamin D₃ to 1,25 dihydroxycholecalciferol.

ACTIONS OF CALCITRIOL (1,25 DHCC)

1. It increases Ca^{2+} (and PO_4^{3-}) absorption from the intestine by (a) Stimulating synthesis of a protein called **calbindin-D** that facilitate Ca^{2+} transport across the intestinal epithelium (b) Increasing the Ca^{2+} - H^+ ATPase in the intestinal cells which is needed to pump Ca^{2+} into the ECF.

2. It facilitates Ca^{2+} reabsorption in the distal tubules of the kidneys.
3. It is necessary for the development of bone (by increasing activity of the osteoblasts), as well as the calcification of bone matrix. *However, in high concentrations, it mobilizes Ca^{2+} and PO_4^{3-} from bone (by secondary increase in the activity of osteoclasts).*
4. It stimulates differentiation of the immune cells (the lymphocytes) which helps production of appropriate immune responses. For this reason, vitamin D deficiency increases the incidence of infections.
5. It stimulates differentiation of keratinocytes in the skin. So vitamin D is useful in the treatment of certain skin diseases.
6. It may be involved in growth regulation & production of growth factors.

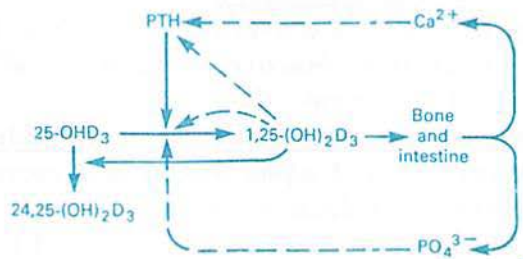


Figure 32 : Control of calcitriol synthesis. Dashed arrows are inhibitory.

REGULATION (CONTROL) OF CALCITRIOL SYNTHESIS

The activity of **1 alpha Hydroxylase enzyme (1 alpha H)** is the main factor in the regulation of calcitriol synthesis. Factors that stimulate this enzyme increase calcitriol synthesis, and vice versa. These factors include the following (figure 32) :

1. **PTH** : This stimulates the (1 alpha H) thus increasing calcitriol synthesis.
2. **Plasma Ca^{2+} level** : When the plasma Ca^{2+} level is high, the secretion of PTH decreases and little calcitriol is synthesized. The opposite occurs when the plasma Ca^{2+} level is low. In the former condition, the kidneys form *the relatively inactive metabolite 24,25 DHCC instead of calcitriol. The adaptation of intestinal calcium absorption (page 78) occurs by this mechanism.*
3. **Plasma PO_4^{3-} level** : As in case of plasma Ca^{2+} , calcitriol synthesis is stimulated by a low and inhibited by a high plasma PO_4^{3-} level (but by a direct effect on the activity of the 1 alpha H in this case).
4. **Hormones** : Prolactin, calcitonin, hCS and growth hormone stimulate calcitriol synthesis. Estrogen increases the total circulating calcitriol level probably due to increasing the amount of its binding protein.
5. **Metabolic acidosis** : This depresses calcitriol synthesis .
6. **Hyperthyroidism** decreases calcitriol synthesis (due to hypercalcemia).

7. The calcitriol plasma level : Its excessive increase leads to (a) Feed-back inhibition of the (1 alpha H) as well as inhibition of PTH secretion (page 74) (b) Stimulation of formation of the relatively inactive metabolite 24,25-DHCC (figure 32).

HYPOVITAMINOSIS D : This decreases intestinal calcium absorption resulting in **hypocalcemia**. The latter leads to excessive secretion of PTH which increases the blood Ca^{2+} level, but it also causes bone demineralization. This results in **rickets** in children, and **osteomalacia** in adults.

Rickets is characterized by **soft bones** (which are easily bent leading to bone deformities) and **dental caries** (and **tetany** when the calcium stores are exhausted). It occurs due to either (a) Deficient intake of vitamin D_3 in the diet or absorption in the intestine e.g. in cases of obstructive jaundice (b) Inadequate exposure to sunlight (c) *Severe renal disease (= renal rickets) in which the kidneys fail to produce 1,25-DHCC* (d) *Congenital deficiency of the 1-alpha hydroxylase enzyme (type I vitamin D resistant rickets)* (e) Congenital defect in the target cell receptors that bind 1,25- DHCC (*type II vitamin D resistant rickets*).

On the other hand, *osteomalacia is less severe than rickets*, and it commonly occurs in women during **pregnancy or lactation**. It differs from **osteoporosis or osteopenia**. In the latter conditions, the protein matrix of bones is deficient leading to bone thinning, while in osteomalacia the protein matrix is normal but poorly calcified.

HYPERVITAMINOSIS D : This produces effects resembling those of **hyperparathyroidism** although PTH secretion is inhibited. The osteoclastic activity increases leading to bone resorption and **osteoporosis**. Plasma Ca^{2+} and PO_4^{3-} levels increase, leading to **polyuria & polydipsia** (due to excessive excretion in urine) and deposition of calcium salts in soft tissues e.g. the lungs, blood vessels and kidneys (so renal failure and hypertension commonly occur).

Other hormones that affect calcium metabolism

1. Glucocorticoids lower the plasma Ca^{2+} level by inhibiting formation & activity of osteoclasts and exerting anti-vitamin D actions. However, prolonged administration stimulates the osteoclasts causing osteoporosis.

2 Growth hormone increases Ca^{2+} excretion in the urine and Ca^{2+} absorption from the intestine. However, the latter effect predominates leading to an increase in the plasma Ca^{2+} level.

3. Thyroid hormones increase Ca^{2+} mobilization from bone. So their excess increases the plasma Ca^{2+} level and may cause osteoporosis.

4. Estrogens help bone development by stimulating osteoblasts and inhibiting osteoclasts (indirectly through stimulating secretion of calcitonin).

5. Insulin stimulates bone growth by its anabolic effect (see chapter 7).

CHAPTER 7

ENDOCRINE FUNCTIONS OF THE PANCREAS (THE ISLETS OF LANGERHANS)

The pancreas is a gland that consists of 2 different types of tissues :
(A) The pancreatic acini : These are *exocrine glands* that secrete the pancreatic juice into the small intestine (refer to digestion).

(B) The islets of Langerhans : These are 1-2 million in number and are *endocrine glands* that make up 1-2 % of the pancreatic mass. They are more plentiful in the tail of pancreas and receive both sympathetic and vagal nerve supply. They contain the following 4 types of cells (figure 33):

1. **A (alpha) cells (20 %) :** These secrete the **glucagon hormone**.
2. **B (beta) cells (60-75 %) :** These secrete the **insulin hormone**.
3. **D (delta) cells (8 %) :** These secrete **somatostatin**.
4. **F cells :** These secrete the **pancreatic polypeptide (PP)**.

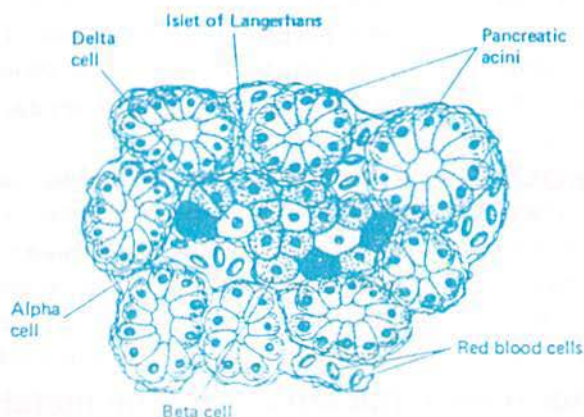


Figure 33 : Histological structure of the pancreas.

INSULIN

Insulin is a *glucose-lowering polypeptide hormone*. Its molecular weight is 5808 and its molecule consists of 2 *chains of amino acids (A and B)* linked by 2 *disulphide bridges* (figure 34). The A chain contains 21 amino acids while the B chain contains 30 amino acids. It is synthesized in the endoplasmic reticulum of the **B cells** from a large **proinsulin** molecule which consists of 3 parts (the A and B chains, and a connecting peptide called **C peptide** which contains 31 amino acids).

Section I- Chapter 7

Endocrine functions of the pancreas

Before secretion, proinsulin is changed to insulin by activity of certain converting enzymes, which separate the C peptides, and **both** insulin as well as the C peptides normally enter the bloodstream (for this reason, *measurement of the C peptide plasma level is useful as an index for the B cell function in patients receiving exogenous insulin*).

The half-life of insulin in the circulation is 5 minutes, and after binding to its receptors and performing its functions, the insulin-receptor complexes aggregate into patches that are taken into the cell by endocytosis (a process called **internalization**). In the lysosomes, insulin is destroyed by protease enzymes while the receptors are broken down or recycled.

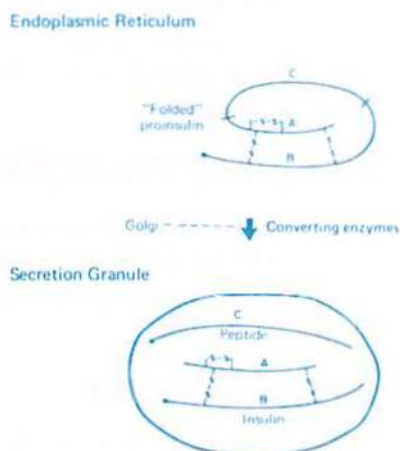


Figure 34 : Synthesis of insulin from proinsulin.

Mechanism of action of insulin (the insulin receptors)

The insulin receptors are complex proteins (each having molecular weight about 340000) that are present *in the membranes of the target cells*. Each is made up of 2 alpha and 2 beta glycoprotein subunits. The alpha subunits are extracellular and bind insulin, while the beta subunits span over the cell membrane and their intracellular portions have **tyrosine kinase activity** (page 6). Binding of insulin triggers the tyrosine kinase activity resulting in autophosphorylation of the beta subunits and this leads to phosphorylation of some cytoplasmic proteins and dephosphorylation of others, which produce the various effects of insulin (see below).

Glucose transport across cell membranes The glucose transporters (GLUTs)

Glucose enters the cells by **facilitated diffusion** i.e. a carrier protein (now called *glucose transporter or GLUT*) moves glucose down its concentration gradient from the ECF into the cells *without need to energy*. These GLUTs are *different from the sodium-dependent glucose transporters* (SGLTs 1 and 2) that are responsible for glucose entrance from the intestinal and renal tubular fluids into their cells by secondary active transport.

7 types of GLUTs were discovered and were numbered from 1 to 7. *The GLUT 4 is the only one that is stimulated by insulin, and is kept in vesicles in the cytoplasm of insulin sensitive cells (see below)*. The other GLUTs are present everywhere in the body but they are insulin-independent. The liver cells contain GLUTs 2 and 7. *GLUT 2 is also present in the B cells of the pancreatic islets, as well as in the intestinal and renal tubular cells, where it transports glucose outside these cells to the ECF (refer to glucose absorption in the GIT and kidney)*.

ACTIONS (EFFECTS) OF INSULIN

Insulin is the **main hypoglycemic hormone in the body**. It also affects the serum K^+ level and is **an anabolic hormone that promotes growth** by increasing the storage of glycogen, fat and protein (so it is also called the *hormone of abundance*).

(1) Effects on carbohydrate metabolism :

Insulin decreases the blood glucose level by the following mechanisms :

a. Enhancing facilitated diffusion of glucose into the cells of the insulin-sensitive tissues (which are rich in GLUT 4). These tissues include *all types of muscles, adipose tissue, bone, skin and other tissues (e.g. mammary glands)*. Binding of insulin to its receptors in these tissues moves the GLUT 4-containing vesicles to the cell membranes, so the number of these transporters increases, which favours glucose diffusion into the cells.

b. Enhancing glucose entry into the liver cells. Insulin stimulates the *glucokinase enzyme* which catalyzes glucose phosphorylation to glucose-6-phosphate. Accordingly, the intracellular free glucose concentration is decreased. This helps glucose diffusion into the liver cells aided by GLUT 2.

c. Increasing glycogen synthesis in the muscles and liver by activating the glycogen synthase enzyme & inhibiting the phosphorylase enzyme.

d. Decreasing glucose output from the liver by increasing glyco-

genesis and inhibiting both gluconeogenesis and glycogenolysis (by inhibiting the gluconeogenic and the glucose-6-phosphatase enzymes).

(2) Effects on fat metabolism :

a. Insulin stimulates *lipogenesis in the liver & adipose tissue* as follows : Under the effect of insulin, the excess glucose in the liver undergoes glycolysis and is transformed into fatty acids, which are released into the circulation as lipoproteins. In the adipose tissue, insulin *activates the lipoprotein lipase enzyme* which releases fatty acids from the lipoproteins. These acids enter the fat cells (adipocytes) where they are esterified with glycerol phosphate (which is formed as a result of metabolism of the glucose that enters the fat cells by the effect of insulin) forming triglycerides which are stored.

b. Insulin *prevents lipolysis in the fat cells* by inhibiting the *intracellular hormone-sensitive lipase enzyme*.

c. Insulin *decreases ketogenesis in the liver* and increases the uptake of ketone bodies by the skeletal muscles.

(3) Effects on protein metabolism :

Insulin exerts an **anabolic effect** by increasing the protein content in the muscles and liver through the following effects :

a. Insulin increases the uptake (transport) of amino acids into the muscle cells and the synthesis of proteins in the ribosomes. It also decreases protein catabolism and the release of gluconeogenic amino acids.

b. Insulin increases protein synthesis in the liver as a result of suppression of gluconeogenesis.

****** Insulin provides an adequate supply of intracellular glucose available for oxidation and production of energy. In this way, **fats are stored in considerable amounts and proteins are spared to promote growth (= sparing action of insulin).**

(4) Effect on growth :

Because of its protein anabolic effect, insulin (with the growth hormone) is essential for normal cellular growth (page 22).

(5) Effect on plasma K^+ level :

Insulin decreases the plasma K^+ level by *increasing K^+ entry into the cells of muscles and adipose tissue* through *activating the Na^+-K^+ ATPase enzyme*. For this reason, high doses of insulin (e.g. for treatment of diabetic ketoacidosis) may lead to hypokalemia. On the other hand, insulin is helpful in treating cases of hyperkalemia.

The principal actions of insulin **in various tissues** are as follows :

(A) **In muscles** : (1) Increasing glucose entry, uptake of amino acids, K^+ & ketone bodies, glycogenesis and protein synthesis (2) Decreasing protein catabolism as well as the release of gluconeogenic amino acids.

(B) **In the liver** : (1) Decreasing both glucose output and ketogenesis (2) Increasing glycogenesis and protein and lipid synthesis (lipoproteins).

(C) **In adipose tissue** : (1) Increasing glucose entry, K^+ uptake, fatty acid & glycerol phosphate synthesis, and triglyceride deposition (i.e. increased lipogenesis) (2) Activation of the lipoprotein lipase enzyme (3) Inhibition of the hormone sensitive lipase enzyme.

**** The most rapid actions** are the increase in the transport of glucose, amino acids and K^+ into the cells, while lipogenesis is a **delayed effect**.

****** The normal fasting plasma insulin level is 0-70 microUnits/ml, and the amount secreted in a normal human is about 40 Units/day.

****** The secretion of insulin increases by factors that increase **cyclic AMP** in the B cells, probably by increasing the intracellular Ca^{2+} content.

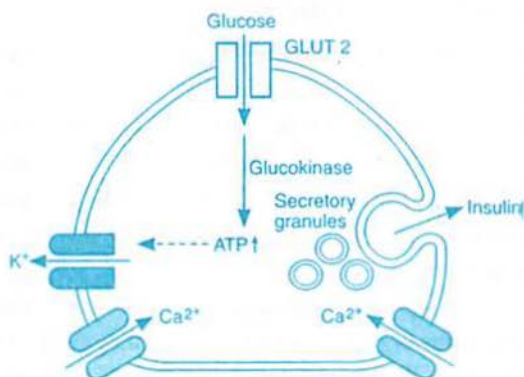


Figure 35 : Mechanism of insulin secretion from the pancreatic islet B cells.

Regulation (control) of insulin secretion

(A) Factors that stimulate insulin secretion

1. Glucose : Hyperglycemia stimulates insulin secretion as follows :

(a) Glucose enters the B cells helped by GLUT 2 (b) Glucose is metabolized, generating **ATP** by oxidative phosphorylation (c) ATP closes the ATP-sensitive K^+ channels, which reduces K^+ efflux (d) This depolarizes the B cells, which activates (opens) voltage-gated Ca^{2+} channels (e) This causes Ca^{2+} influx from the ECF, which causes insulin secretion by exocytosis of the secretory granules (figure 35).

2. Amino acids : Certain amino acids (e.g. *arginine and leucine*) stimulate insulin secretion like glucose i.e. by generating ATP when metabolized (see above). In addition, *arginine is the precursor of NO*, which also stimulates insulin secretion.

3. Ketone bodies : The beta keto acids (e.g. acetoacetic acid) also stimulate insulin secretion like glucose (by generating ATP when metabolized).

4. Parasympathetic stimulation : Stimulation of the right vagus nerve (which innervates the pancreatic islets) increases insulin secretion through releasing **acetylcholine** which acts by stimulating certain muscarinic receptors (M_4) at the B cells.

5. G.I.T. hormones : Many GIT hormones stimulate insulin secretion e.g. secretin, gastrin, CCK and GIP (gastric inhibitory peptide). *The latter (GIP) is the most powerful, and it seems that its main function is stimulation of insulin secretion and not inhibition of the gastric activities.*

****** Recently, a more powerful insulinotropic gut factor than GIP was identified. It was found to be a **glucagon-like polypeptide (GLP)**. There are receptors for both GIP and GLP on the B cells, and both act by increasing the Ca^{2+} influx into these cells via voltage-gated Ca^{2+} channels.

6. Glucagon : This hormone stimulates insulin secretion by increasing the cyclic AMP in the B cells, and also by causing hyperglycemia.

7. Drugs : The sulphonylurea group of drugs stimulate insulin secretion by the same mechanism of glucose i.e. by inducing ATP formation in the B cells (see above). Other drugs that stimulate insulin secretion act by increasing the *cyclic AMP in the B cells* e.g. the beta-adrenergic stimulating drugs and theophylline (the latter inhibits the phosphodiesterase enzyme, thus preserving cAMP).

(B) Factors that inhibit insulin secretion

1. Somatostatin.

2. K^+ depletion, so conditions of hypokalemia (e.g. due to Conn's syndrome or prolonged use of thiazide diuretics) decrease glucose tolerance.

3. 2-deoxyglucose and mannoheptulose : These substances prevent glucose metabolism in the B cells, leading to inhibition of insulin secretion.

4. Exogenous insulin : This inhibits pancreatic secretion of insulin through a negative feedback mechanism and also by causing hypoglycemia.

5. Alloxan : This substance selectively destroys the B cells leading to decreased insulin secretion and diabetes (= *alloxan diabetes*).

6. Drugs e.g. the thiazide diuretics, diazoxide, phenytoin, *alpha-adrenergic receptor stimulators and beta adrenergic receptor blockers.*

7. Sympathetic stimulation (see next).

****** The islet B cells contain both α_2 and β_2 adrenergic receptors. **The alpha receptors are inhibitory for insulin secretion** (because they decrease the intracellular cyclic AMP content) **while the beta receptors are stimulatory** (because they increase the intracellular cyclic AMP content). **However, the alpha receptors normally predominate, so the net result of sympathetic stimulation is inhibition of insulin secretion.**

****** A polypeptide called **galanin** is found in some of the autonomic nerves that supply the islets of Langerhans. It inhibits insulin secretion by **activating (opening) the K^+ channels** (see above).

GLUCAGON

Glucagon is a **polypeptide hormone** (consisting of 29 amino acids and having m.w. 3485), that is secreted by the **A (alpha) cells of the pancreatic islets**. Its half life is 5-10 minutes and it acts mainly by increasing formation of **cyclic AMP** in the target cells (page 8).

Actions (effects) of glucagon

1. It is a **hyperglycemic hormone** (i.e. it increases the blood glucose level) by **increasing glucose output from the liver** (through stimulating both **glycogenolysis and gluconeogenesis**).
2. It **increases lipolysis in adipose tissue** which leads to increased formation of ketone bodies in the liver (so it is **lipolytic and ketogenic**).
3. It elevates the metabolic rate (= **calorigenic action**) probably due to the increased hepatic deamination of amino acids.
4. It exerts a **positive inotropic effect on the heart** (without increasing the myocardial excitability).
5. It stimulates secretion of the growth hormone (page 19), insulin (page 89) and the pancreatic somatostatin.
6. It produces some effects on the GIT e.g. it inhibits gastric secretion.

****** The main function of glucagon in physiological doses is its hyperglycemic effect, which supplies energy substrate to the tissues (so it is an **energy releasing hormone**). Its other functions require much higher doses, specially its lipolytic, ketogenic and cardiac effects (see above).

Regulation (control) of glucagon secretion

(A) Factors that stimulate glucagon secretion

1. Decreased blood glucose level (**hypoglycemia**).
2. Amino acids, specially the **glucogenic ones** eg alanine, glycine,

serine and cysteine (which are converted to glucose by effect of glucagon).

3. Certain GIT. hormones, specially **CCK and gastrin**.
4. **Cortisol** (the major glucocorticoid).
5. **Exercise, infections and other stresses** (e.g. starvation) probably *due to increased sympathetic stimulation* (see below).
6. **Acetylcholine** (so **vagal stimulation increases glucagon secretion**).
7. **Drugs** e.g. theophylline and beta-adrenergic receptor stimulators (see below).

(B) Factors that inhibit glucagon secretion

1. Increased blood glucose level, due to release of GABA from the beta cells (together with insulin) which inhibits the alpha cells.
2. Somatostatin and insulin.
3. Certain G.I.T. hormones, specially secretin.
4. Increased plasma level of free fatty acids (FFAs) or ketone bodies.
However, this is not always the case e.g. in diabetic ketoacidosis, glucagon secretion is not inhibited and its plasma level is high (page 94).
5. **Drugs** e.g. phenytoin and alpha-adrenergic receptor stimulators.

. ****** Like the B cells, the islet A cells also contain both α_2 and β_2 adrenergic receptors, and the α receptors are inhibitory for glucagon secretion while the β receptors are stimulatory. However, unlike the B cells, the β receptors normally predominate, so *the net result of sympathetic stimulation (or adrenaline) is glucagon secretion*.

Accordingly, **stimulation of both parasympathetic and sympathetic nerves increase secretion of glucagon.**

SOMATOSTATIN

This hormone exerts **only inhibitory effects** at the sites of its release which include **(a) The pancreas**, where it inhibits the release of the other pancreatic hormones (insulin, glucagon and the PP) **(b) The GIT**, where it inhibits its motility and secretion (see last page in digestion) **(c) The hypothalamus**, where it inhibits growth hormone secretion (page 15).

THE PANCREATIC POLYPEPTIDE (PP)

This consists of 36 amino acids, and its secretion is stimulated by a high protein meal, exercise, fasting and hypoglycemia as well as by parasympathetic stimulation. It slows food absorption in the GIT, but its exact physiological significance is unknown.

REGULATION OF THE BLOOD GLUCOSE LEVEL (GLUCOSE HOMEOSTASIS)

The **blood glucose content is normally variable**, depending on the balance between the amount of glucose entering the bloodstream and the amount leaving it. However, such variability is normally limited by certain regulatory mechanisms which prevent its rise more than 150 mg/dL after carbohydrate-rich meals and its fall below 60 mg/dL after prolonged starvation (dL = 100 ml). In the postabsorptive state (12 hours after the last meal), the blood glucose level in peripheral venous blood averages 90 mg/dL, ranging from **70 to 110 mg/dL**, and it is *normally higher by 15 - 30 mg/dL in arterial blood*. This is called **fasting blood glucose**, and it is frequently measured for detection of disorders in carbohydrate metabolism.

The organs that **add glucose to the blood besides the GIT** are (1) *The liver (through glycogenolysis and gluconeogenesis)* (2) *The kidneys (which are reported to be capable of gluconeogenesis, but only in cases of prolonged starvation)*.

On the other hand, the organs that **remove glucose from the blood** include (1) *The liver and skeletal muscles, through glucose uptake and glycogenesis* (2) *Adipose tissue, through glucose uptake and lipogenesis* (3) *The kidneys, through excreting glucose in the urine if its blood level exceeds a certain threshold known as the renal threshold for glucose (about 180 mg/dL)* (4) *Other tissues particularly the blood cells and brain (in which the fuel that can be used is only glucose)*. After a carbohydrate-rich meal, 5-10 % of the ingested glucose is changed into glycogen in the liver (which contains about 100 gm glycogen), 30-40 % is converted into fat in adipose tissue, 30-40 % enters the muscles (to be stored in the form of glycogen) while the remainder is metabolized in other tissues.

THE GLUCOSE REGULATORY MECHANISMS

(1) HEPATIC REGULATION

The liver acts as a **glucostat** by (a) Removing excess glucose from the blood when its level increases after meals and converting it into glycogen (= **glycogenesis**) (b) Addition of glucose to the blood when its level decreases between meals, first through **glycogenolysis** then through **gluconeogenesis after exhaustion of the liver glycogen** (the liver stores about 100 gm glycogen that *supplies glucose for only 6-8 hours*).

Such glucostatic functions of the liver are controlled by numerous hormones (see next), although they are induced to a little extent directly by

the changes in the blood glucose level independent of the hormones (= *autoregulation by the blood glucose level*).

(2) HORMONAL REGULATION

The glucoregulatory hormones include the following :

1- Insulin : This is almost the *only glucose-lowering hormone* in the body. It is secreted if the blood glucose level increases in order to prevent hyperglycemia through (a) Increasing glucose uptake by the tissues (b) Decreasing glucose output from the liver (page 86).

2- Anti-insulin hormones : These are the **growth hormone** (page 18), **cortisol** (page 51), **catecholamines** (page 68) and **glucagon** (page 90). The actions of these hormones are opposite to those of insulin. They are *glucose-raising hormones*, and they are secreted if the blood glucose level decreases in order to prevent hypoglycemia through (a) Stimulating release of glucose from the liver into the bloodstream (b) Decreasing glucose uptake by the tissues.

(3) RENAL REGULATION

The kidneys act only in certain situations. Their ability of gluconeogenesis and addition of glucose to the blood is significant only in cases of prolonged starvation. On the other hand, they can remove glucose from the blood in cases of hyperglycemia and its excretion in the urine only if the blood glucose level exceeds the renal threshold of 180 mg /dL (see above).

(4) NEURAL REGULATION

Sympathetic stimulation increases glycogenolysis in the liver which increases the hepatic glucose output, resulting in **elevation of the blood glucose level**. It is doubtful whether parasympathetic stimulation produces an opposite effect.

The effect of sympathetic stimulation is important in cases of hypoglycemia. In such cases, certain glucoreceptors in the hypothalamus are stimulated, resulting in activation of the sympathetic system as well as release of catecholamines from the adrenal medullae (page 71) which increase the blood glucose level. In addition, excitation of the sympatho-adrenal system *stimulates secretion of glucagon and inhibits secretion of insulin* (see above), and these effects also help elevation of the blood glucose level.

DIABETES MELLITUS (DM)

DM results from **decreased actions of insulin**. This rarely occurs due to genetic defects in the insulin molecule itself, the insulin receptors or

the GLUT 4. DM may also occur secondary to excessive secretion of the anti-insulin hormones *e.g. in Cushing's syndrome and acromegaly* (= **secondary DM**). However, most cases belong to one of the following types:

1. Type I or insulin-dependent DM : This type is also called **Juvenile DM** because it occurs in young ages. It is a *T lymphocyte - mediated (or autoimmune) disease* in which antibodies against the B cells are formed leading to their destruction, with eventual absence of insulin in the blood.

2. Type II or noninsulin-dependent DM : This type is also called **Maturity-onset DM** because it usually occurs after the age of 40 years, and is almost always associated with **obesity**. The patients usually have normal B cells morphology and their *plasma insulin levels are normal or elevated* (except in long-standing cases). However, the defect lies in **presence of insulin resistance** *i.e. decreased sensitivity of the tissues to insulin*.

Lack of insulin activity leads to **(1) Decreased entry of amino acids into the muscles** **(2) Increased lipolysis in adipose tissue** **(3) Reduced entry of glucose into the cells and increased hepatic glucose output** (= *gluconeogenesis*) resulting in **hyperglycemia**. *Glucagon is also usually increased which increases the hyperglycemia by inducing gluconeogenesis*. Other anti-insulin hormones also contribute when the stress of illness is severe. Accordingly, there will be **starvation in the midst of plenty** (*i.e. intracellular glucose deficiency with extracellular glucose excess*), and the fasting blood glucose level is elevated usually more than 140 mg/dL, and frequently it may exceed its renal threshold (180 mg/dL) resulting in **glucosuria**.

LEPTIN AND THE OTHER ADIPOKINES

It was suggested that a chemical signal from the adipose tissue increases insulin resistance because of the common observation that **weight reduction frequently improves DM**. This seems to be true, since recently several substances that are *secreted by the fat cells and affect insulin resistance* were identified. They are called **adipokines e.g. leptin and resistin** (the former decreases insulin resistance while the latter increases it). Leptin is a **satiety-producing protein hormone**, consisting of 167 amino acids, and it decreases the food intake and also increases the energy consumption.

SYMPTOMS (MANIFESTATIONS) OF DM

1. Polyuria : This occurs due to **glucosuria** which produces *osmotic diuresis* (see table in page 30) . It causes loss of Na^+ , K^+ and water-soluble vitamins in the urine, and *muscle cramps may occur due to hyponatremia*. Severe cases also lead to *dehydration, hypovolemia and hypotension*.

2. Polydipsia (= excessive drinking of water) due to an increased *sensation of thirst* that results from **(a) Reduction of the ECF volume** secon-

dary to polyuria (b) Plasma hyperosmolality produced as a result of hyperglycemia (refer to the mechanisms of thirst in blood and kidney).

3. Hyperphagia or polyphagia (= increased appetite & food intake) due to deficient glucose utilization *in the cells of the satiety centre in the hypothalamus* secondary to insulin deficiency (which decreases the activity of this centre, so the feeding centre operates unopposed resulting in polyphagia).

4. Muscle wasting and rapid fatiguability : Muscle wasting occurs secondary to *protein depletion* caused by the increased protein catabolism. This, together with inability of the muscles to utilize glucose due to insulin deficiency, render the patient to be *tired and rapidly fatigued*.

5. Loss of weight due to both muscle wasting and depletion of the fat depot stores in the body (see below).

6. Decreased resistance to bacterial infections : The patient is susceptible to infections (specially in the skin and external genitalia) due to both the protein deficiency and the hyperglycemia (*the sugar-rich body fluids are good media for bacterial activity*).

7. Visual manifestations : Hyperglycemia causes visual disturbances which vary from just changing the refractive power of the various optic media (which decreases the visual acuity) to *microvascular changes in the retina* which may lead to its scarring (*diabetic retinopathy*) resulting in blindness.

8. Increased lipolysis : This leads to depletion of the fat stores and causes (a) *Lipemia* (increased blood levels of FFAs and triglycerides) , which predisposes to fatty liver degeneration (b) *Increased plasma cholesterol level* which predisposes to atherosclerosis in long-standing cases (c) *Increased blood level of ketone bodies (= ketosis or ketonemia)* which are organic acids (= *ketoacids*) that cause acidosis. They include *acetoacetic acid* and its derivatives {*beta hydroxybutyric acid and acetone*). They are formed in the liver as a result of FFAs catabolism to acetyl-CoA and when they exceed a certain blood level, they are excreted in the urine (= *ketonuria*). These effects are so prominent that diabetes is sometimes described to be "*more a disease of lipid than of carbohydrate metabolism*".

9. Acidosis : This occurs in severe cases due to excess ketosis and the blood pH may be lowered (= *acidemia*), although the buffering mechanisms are acting (refer to kidney). In addition, lactic acid is liberated in excess from the tissues as a result of their hypoxia (due to dehydration) leading to *lactic acidosis* (which worsens the acidemia due to ketosis).

10. Coma : The plasma hyperosmolality due to hyperglycemia causes dizziness and even unconsciousness or coma due to dehydration of the brain cells (*hyperosmolar coma*). However, in the terminal stage of the disease coma (which is often fatal) occurs because of the combined effects of *acidosis, dehydration and plasma hyperosmolality* on the nervous system.

CHAPTER 8

THE PINEAL GLAND (THE EPIPHYSIS)

The pineal gland arises from the **roof of the 3rd ventricle of the brain** and it was believed to be **the seat of the soul**. It is innervated by **sympathetic postganglionic fibres** (= **nervi conarii**) that arise from the *superior cervical ganglia* (refer to autonomic N.S.). It is **large in youngs**, but it begins to involute before puberty with deposition of *calcium salts* (which appear in X-ray as **pineal sand**) and its *secretion declines gradually with age*. Histologically, it consists of neuroglia and parenchymal secretory cells called **pinealocytes** which secrete a hormone called **melatonin**.

MELATONIN (N -Acetyl-5-methoxytryptamine)

This is a hormone that **lightens the skin of tadpoles** (by an action on melanophores) *but not mammals*, and is synthesized from **serotonin**. It is secreted by the pineal gland and, to a little extent, also by certain other organs. The extra-pineal melatonin is *tonically secreted* to maintain a constant blood level, but in contrast to the pineal melatonin, it is not affected by light, age or nervous stimulation (see below).

Regulation of melatonin secretion : The secretion of *pineal melatonin* is **increased by sympathetic stimulation** (via *beta adrenergic receptors* in the gland), and shows a characteristic **light-dark circadian rhythm**. It **increases on exposure to darkness and decreases during day-light hours**. This occurs through *influencing the sympathetic discharge to the gland* as follows : Signals discharged via **retino-hypothalamic nerve fibres** affect the activity of the **hypothalamic suprachiasmatic nuclei** (*the biologic clock in the body*), which control the sympathetic activity to the gland via **hypothalamo-spinal fibres** that terminate at the lateral horn cells in the upper thoracic segments of the spinal cord, from which preganglionic fibres arise and reach the superior cervical ganglia (the origin of the *nervi conarii*).

Functions of melatonin : There are **no established functions for melatonin in mammals**. The diurnal variation in melatonin secretion probably functions as a **timing device that keeps internal events synchronized with the light-dark cycle in the environment**. It is also reported that it (a) **Inhibits gonadal functions and LH secretion** (b) **Delays the onset of puberty**, because *pineal damage* (e.g. by tumours) is sometimes associated with *sexual precocity*. However, this was found to occur only when *such tumours cause hypothalamic damage as well* (page 102). In addition, it induces sleep and produces a sense of well-being (so it is sometimes used in the treatment of certain cases of depression).

SECTION II

REPRODUCTION

CHAPTER 1

SEXUAL DEVELOPMENT AND PUBERTY

The sex organs include the **gonads or primary sex organs** (which are 2 *testes in males and 2 ovaries in females*) as well as the other sex organs (= **secondary or accessory sex organs**). The gonads are controlled by the **gonadotropic hormones** and they perform 2 functions :

1. Gametogenesis i.e. production of gametes (= germ cells) : This includes *spermatogenesis in the males* (= production of sperms) and *oogenesis in the females* (= production of ova).

2. Secretion of sex hormones (so the gonads are *endocrine glands*).

GAMETOGENESIS

The sperms and ova are formed from primitive germ cells present in the gonads called *spermatogonia* in the testes and *oogonia* in the ovaries. These cells, like the somatic cells in the body, contain a **diploid number of chromosomes** (46 chromosomes) which include 44 *somatic chromosomes* (= *autosomes*) and 2 *of the sex chromosomes* (the X and Y chromosomes). Spermatogonia contain one X and one Y chromosome (XY pattern) whereas the oogonia contain 2 X chromosomes (XX pattern).

SPERMATOGENESIS

The spermatogonia **proliferate then grow** into *primary spermatocytes* which contain the diploid number of chromosomes i.e. 46 chromosomes (44 autosomes, and one X and one Y chromosome). The primary spermatocytes then **mature** through *meiosis* (= *reduction division*) then mitosis as follows : Each primary spermatocyte undergoes meiotic division producing 2 *secondary spermatocytes* (each containing only a *haploid number of chromosomes* i.e. 23 chromosomes, 22 autosomes and one sex chromosome, the X or the Y), then by mitotic division, each secondary spermatocyte divides into 2 spermatids (that also contain a haploid number of chromosomes) and these are then **transformed** into *mature spermatozoa* by a process known as **spermiogenesis**. Therefore, *from each primary spermatocyte, 4 spermatozoa are formed* (figure 36). Through proliferation of the spermatogonia, it was estimated that **512 spermatids are formed from a single spermatogonium**.

****** The control of the **4 stages of spermatogenesis** (the *proliferative, growth, maturation and transformation stages*) will be discussed in the male reproductive system.

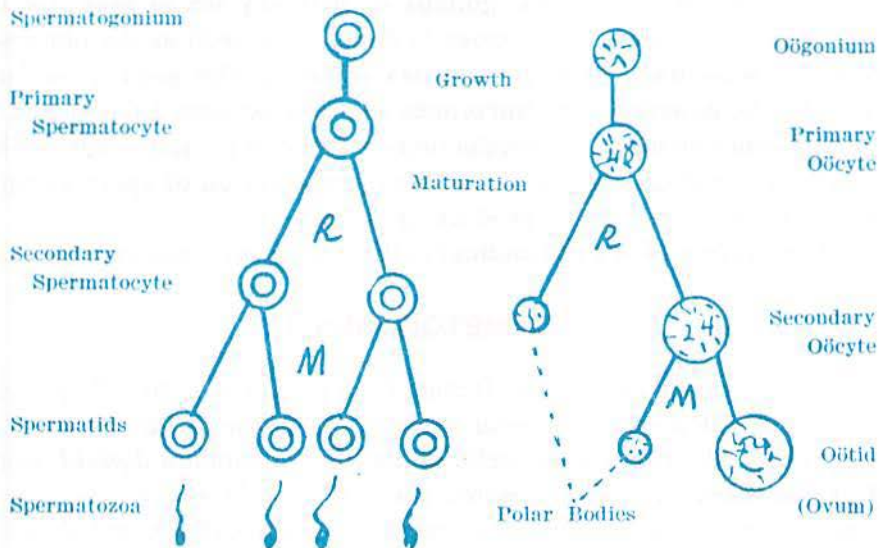


Figure 36 : Spermatogenesis (left) and oogenesis (right). R = reduction division (meiosis). M = mitotic division.

OÖGENESIS

The oögonia grow into *primary oocytes* which contain the diploid number of chromosomes i.e. 46 chromosomes (44 autosomes and 2 X chromosomes) then through meiosis, each primary oocyte divides producing *a secondary oocyte and the first polar body* (each containing only a haploid number of chromosomes i.e. 23 chromosomes (22 autosomes and one X chromosome)). The first polar body degenerates while the secondary oocyte by a mitotic division, produces *an oötid* containing a haploid number of chromosomes (which develops into the mature ovum) and the *second polar body* (which also degenerates). In this way, *each primary oocyte produces only one mature ovum* (figure 36).

When the ovum is fertilized by a sperm, a cell with a **diploid number of chromosomes** is formed (= zygote) and sex is then determined by presence or absence of the Y chromosome (see next). If the sperm was containing a Y chromosome, an XY pattern results and the zygote develops into a male, while if it was containing an X chromosome, an XX pattern results and the zygote develops into a female.

SEXUAL DEVELOPMENT AND DIFFERENTIATION

Until the 6th week of pregnancy, the primitive fetal gonads (which are formed near the adrenal glands) are identical in both sexes and are **bi-potential** i.e. they can be differentiated into either testes or ovaries. Each of these gonads is formed of a **cortex and a medulla**. In genetic males, the medulla develops into a testis and the cortex regresses, while in genetic females, the cortex develops into an ovary and the medulla regresses. **Gonadal differentiation occurs during the 7th and 8th weeks**, and at this time, the embryo also forms both male and female **primordial genital ducts**. The female genital ducts are called **Mullerian ducts** while the male genital ducts are called **Wolffian ducts**, and both open externally together with the urethra at the **urogenital slit**. Sex determination depends on the **presence or absence of the Y chromosome** as follows :

(1) In presence of the Y chromosome (i.e. in genetic males), the testes are formed because the Y chromosome causes testicular differentiation from the medulla of the primitive gonads (see above), and the product of the testes-determining gene is called **SRY** (= Sex-determining Region of the Y chromosome). The embryonic testes secrete (a) **Mullerian inhibiting substance (MIS) by the Sertoli cells** (page 105), which causes regression of the Mullerian ducts by *apoptosis* (= programmed cell death) so female genital organs do not develop (b) **Testosterone by the Leydig cells** (page 104) under influence of a hormone called **human chorionic gonadotropin** (page 137). Testosterone causes the following : (a) Development of the Wolffian ducts which consequently develop into the *male internal genital organs* (epididymis, vas deferens and seminal vesicles) (b) Closure of the urogenital slit and formation of the male external genital organs (by its metabolite called *dihydrotestosterone*, page 111) (c) Development of the brain, and such early exposure of the brain to testosterone may be the *cause of the male pattern of sexual behavior at puberty*.

(2) In absence of the Y chromosome (i.e. in genetic females), no testes are formed and instead, the ovaries develop from the cortex of the primitive gonads (see above) *but they do not secrete hormones*. Due to absence of MIS, the Mullerian ducts develop and form the female internal genital organs (uterus and fallopian tubes) as well as the upper part of the vagina, while the Wolffian ducts regress due to absence of testosterone. The **urogenital slit remains open** and the female external genital organs (vulva and labia majora and minora) as well as the lower part of the vagina will subsequently be formed.

****** Since development of the external genital organs in both sexes occurs after gonadal differentiation, these organs also remain bi-potential until the 8th week of development, after which they are differentiated.

****** The human *Y chromosome is smaller* than the X chromosome, so the sperms having Y chromosomes are lighter and swim faster in the female genital tract than those having X chromosomes, and thus can reach the ova more rapidly. *This may explain why the number of born males is normally slightly greater than the number of females.*

ABNORMAL SEXUAL DIFFERENTIATION

(A) Chromosomal abnormalities

(1) Nondisjunction

This is a defect in gametogenesis in which the pair of sex chromosomes *fail to separate during meiosis*, so that both go to one of the daughter cells while the other cell will contain O (zero) sex chromosome. Therefore, in the process of fertilization, zygotes having abnormal chromosomal patterns will be produced *e.g. during oogenesis, if some of the ova contain the 2 X chromosomes while others contain O sex chromosome, the following abnormalities may be produced on fertilization :*

1. XXY pattern : This occurs as a result of fertilization of an ovum containing 2 X chromosomes by a sperm containing a Y chromosome. It is **the commonest disorder** and is called **Klinefelter syndrome**. The patient has the genitalia of a normal male (and develops male characters) but his seminiferous tubules are abnormal (so the condition is called **seminiferous tubule dysgenesis**) and there is also mental retardation.

2. XXX pattern : This occurs as a result of fertilization of an ovum containing 2 X chromosomes by a sperm containing an X chromosome. Such case is called **superfemale** and is not associated with any characteristic abnormalities (so it usually passes unnoticed).

3. XO pattern : This occurs as a result of fertilization of an ovum containing O sex chromosome by a sperm containing an X chromosome. Such case is called **Turner syndrome, ovarian agenesis or gonadal dysgenesis**. The gonads (ovaries) are rudimentary, stature is short, other congenital abnormalities are often present, and puberty is delayed or absent.

4. YO pattern : This occurs as a result of fertilization of an ovum containing O sex chromosome by a sperm containing a Y chromosome. Such condition is **lethal (= fatal) due to lack of the X chromosome** (which carries essential genetic informations for the normal fetal development).

(2) Mosaicism

This is a pathological condition that results from *faulty mitoses in the early zygote*, producing an individual with 2 or more different

chromosomal patterns. Such individual is called a **mosaic** e.g. **XX/XY mosaicism** (which may be associated with **true hermaphroditism** i.e. an individual that has both types of gonads).

(B) Hormonal abnormalities

The commonest hormonal sexual abnormality is **pseudohermaphroditism**. This is a condition in which an individual has the genetic constitution and gonads of one sex *but the external genitalia of the other*. There are **2 types** of this condition :

1. Female pseudohermaphroditism : This is development of male external genitalia in females. It occurs when a female fetus is exposed to excess androgens during the 8th -13th weeks of pregnancy, commonly due to **a congenital virilizing adrenal tumour** (page 64) or as a result of excessive doses of androgens given to the mother.

****** *After the 13th week of pregnancy, the genitalia are almost completely formed and exposure of the female fetus to androgens can cause only hypertrophy of the clitoris.*

2. Male pseudohermaphroditism : This is development of female external genitalia in males. It occurs when development of the **embryonic testes is defective or if there is androgen resistance** (= a condition in which testosterone is secreted from the testes, but it is unable to exert its effects). Such resistance is usually due to either absent or abnormal androgen receptors, but **deficiency of the 5 alpha - reductase enzyme** (which converts testosterone to another important active form called **dihydrotestosterone**) may also be a cause (page 112).

PUBERTY

The gonads remain quiescent (= silent) until adolescence, and at that time they become activated by the GTHs. *Puberty is the time when the endocrine and gametogenic functions of the gonads are developed enough so that reproduction becomes possible*. The normal range of age at which puberty occurs (in USA) is **8-13 years in girls and 9-14 years in boys**.

MECHANISM (CONTROL) OF ONSET OF PUBERTY

In children, the anterior pituitary gland contains GTHs, but they are not secreted although the hypothalamus contains GnRH. It seems that a **neural mechanism prevents the release of GnRH**, and puberty sets in when

such mechanism fails. However, the nature of this mechanism and the cause of its failure are unknown.

Relation of puberty to leptin (= the satiety-producing hormone)

It was recently reported that a critical body weight must be reached for puberty to occur. It appears that leptin (page 94) may be the link between the body weight and puberty since obese mice that lack leptin are infertile and leptin treatment induces precocious puberty in immature female mice.

ABNORMAL PUBERTY

(A) Precocious puberty (sexual precocity) : This is 2 types :

1. Precocious pseudopuberty : This is an early development of the secondary sex characteristics and accessory sex organs but *without gametogenesis* (i.e. there is no spermatogenesis or oogenesis). It occurs as a result of an *abnormal oversecretion of androgens in immature males or estrogens in immature females*. In males, the condition may be due to either an *androgen-secreting tumour of the adrenal cortex* (page 64), or a *tumour in the Leydig cells of the testis* (which secretes excess testosterone). On the other hand, in females, the condition may result from either an *estrogen-secreting tumour of the adrenal cortex*, or a *granulosa cell tumour of the ovary* (which secretes excess estrogens).

2. True precocious puberty : This is a true premature puberty (i.e. accompanied by both sexual development and gametogenesis) that occurs in young ages as a **result of early secretion of GTHs**. In some cases, it is *constitutional in nature*, but in most cases it is due to *hypothalamic disorders that are associated with increased secretion of GnRH* (e.g. tumours or infections). Some cases are not initiated by GnRH secretion (= **gonadotropin-independent precocity**). Tumours of the pineal gland are sometimes also associated with sexual precocity, but this was found to occur only when there is secondary damage of the hypothalamus (page 96).

(B) Delayed (or absence of) puberty

Puberty is considered to be pathologically delayed in females when the *menarche* (= *first menstruation*) *does not occur by the age of 17 years*, and in males *when testicular development fails to occur by the age of 20 years*. The condition may occur as a result of **panhypopituitarism**, **Turner syndrome** (page 100) or **cretinism** (page 45), but however, in some individuals puberty is delayed *without an apparent cause*. Such cases are called **eunuchoidism in males and primary amenorrhea in females**.

CHAPTER 2

THE MALE REPRODUCTIVE SYSTEM

The male organs of reproduction include the following (figure 37) :

(1) The testes (male gonads) : These constitute the *primary sex organs*, and are concerned with *spermatogenesis* and secretion of 3 hormones (a) *Testosterone* (b) *Inhibin* (c) Small amounts of *estrogen* (see below)

(2) The accessory (or secondary) sex organs : These include :

a. The epididymes : Each epididymis is a single long coiled tube in which the sperms are stored and become more mature.

b. The vasa deferens : Each vas is a long muscular duct that conducts the sperms from the epididymes to the urethra by peristaltic movements.

c. The seminal vesicles : Each vesicle is a gland that secretes viscid fluid rich in fructose, prostaglandins, ascorbic acid and flavins. Their ducts join the ends of the vasa deferens forming the *ejaculatory ducts* which pass through the prostate and open into the prostatic portion of the urethra.

d. The prostate : This is a large gland that surrounds the upper part of the urethra. It secretes an alkaline fluid during intercourse that contains citric acid, Ca^{2+} and proteolytic enzymes.

e. The bulbourethral (Cowper's) glands : These secrete mucus during intercourse which neutralizes the acidity inside the urethra and lubricates the sexual movements.

f- The penis : This is formed of *erectile tissue* that can accommodate a great amount of blood by V.D. resulting in its erection (which is essential for introduction of the seminal fluid deep into the female genital tract).

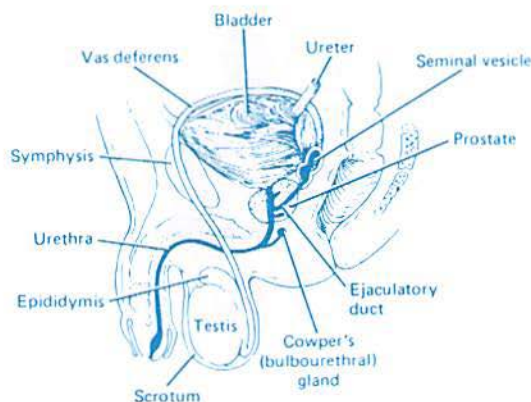


Figure 37 : The male reproductive system.

STRUCTURE AND FUNCTIONS OF THE TESTES

Each testis is made up of **2 specialized types of tissues** (figure 38) :

(A) Seminiferous tubules : These are concerned with formation of spermatozoa (i.e. spermatogenesis) and they contain **2 types of cells** :

1. **The cells concerned with spermatogenesis** (spermatogonia, primary and secondary spermatocytes and spermatids).

2. **The Sertoli cells** : These are large cells located between the germ cells and they are rich in glycogen which is used for nutrition of the sperms. They are **stimulated by FSH**, and perform several functions (see next page).

(B) Interstitial cells of Leydig : These cells are located between the seminiferous tubules, and their function is the **synthesis and secretion of the testicular androgen** (= **testosterone**).

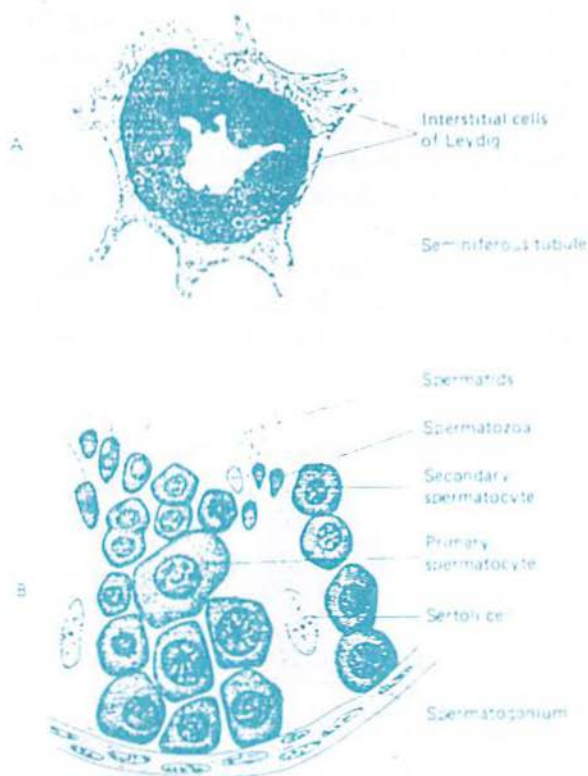


Figure 38 : (A) Cross-section in a seminiferous tubule. (B) Formation of spermatozoa by the germinal epithelium.

Functions of the Sertoli cells

1. Nutrition and maturation of the spermatids in deep folds in their cytoplasm and their transformation into spermatozoa (= **spermiogenesis**).

2. They secrete the following substances :

a. **Androgen-binding protein (ABP)** : This maintains a high concentration of androgen (testosterone) in the seminiferous tubular fluid, which is essential in the process of spermatogenesis (see below).

b. **Inhibin** (a hormone that inhibits FSH secretion from the anterior pituitary gland) and a small amount of **estrogens** (androgens diffuse from the Leydig cells to the Sertoli cells which contain the **aromatase enzyme that converts androgens to estrogens**).

c. **Mullerian-inhibiting substance or MIS** (page 99) which causes regression of the Mullerian ducts in males during fetal life (so it is also called **Mullerian regression factor or MRF**). The MIS also induces **descent of the testes to the inguinal region** (page 107).

3. The tight junctions between adjacent Sertoli cells near the basal lamina form a **blood-testis barrier which prevents** :

a. Many large molecules to pass from the interstitial tissue to the tubular lumen (thus **protecting the germ cells from many noxious agents**).

b. Antigenic products of germ cell division from entering the circulation (thus protecting against development of **autoimmune responses**).

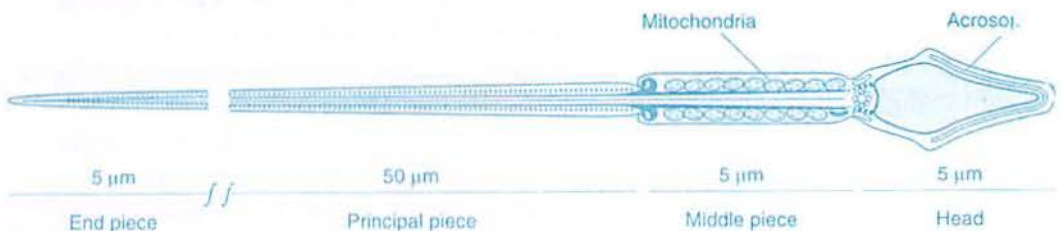


Figure 39 : A human spermatozoon.

The spermatozoa (or sperms)

In humans, it takes about *74 days to form a mature sperm*. The human sperm is a single motile cell formed of a head and a long tail (figure 39). The head is composed mainly of a nucleus made up mostly of chromosomal material (DNA), and its anterior part is covered by a lysosome-like organelle called **acrosome** (which contains a number of *proteolytic enzymes that help the sperm to penetrate and fertilize the ovum*, page 135).

Spermatozoa leaving the testes are not fully motile, and they continue maturity and acquire motility *in the epididymis*. Their **progressive motility** is produced by *movement of their tails* and involves activation of a special protein localized there called **Catsper**. Normal sperms move at a speed of about 3 mm/minute in the female genital tract. They reach the uterine tubes 30-60 minutes after ejaculation and **remain active for about 48 hours** (however, they can live for much longer times *in vitro* if they were kept at lower temperatures than 37 °C e.g. in *semen banks*).

Sperm capacitation : This is a process of further maturation of the sperms that occurs in the female genital tract after ejaculation. It takes 2-8 hours and involves a marked increase of both the sperms' motility and their ability for fertilization (by *facilitating the acrosomal reaction*, page 135).

Factors that control (affect) spermatogenesis

In addition to **healthy testicular germinal epithelium and the role played by the Sertoli cells**, the following factors affect spermatogenesis :

(1) HORMONES

(A) Anterior pituitary gonadotropic hormones (GTHs) :

1. **FSH** : This acts on the **Sertoli cells** to facilitate the last stages of spermatid maturation (**spermiogenesis**). It also **maintains a high concentration of testosterone in the seminiferous tubular fluid** (which is essential for normal spermatogenesis) by (a) Promoting secretion of the **ABP** from the Sertoli cells (b) *Sensitization of the Leydig cells to the action of LH* (see next).

2. **LH** : This stimulates *testosterone secretion* from the interstitial cells of Leydig (so it is called the **interstitial cell-stimulating hormone or ICSH**).

(B) **Testosterone** : This hormone is secreted from the Leydig cells under the effect of LH, and it reaches the seminiferous tubules directly where it is maintained at a high concentration by the effect of the **ABP** (see above). It is essential for the maturation phase of spermatogenesis particularly spermatid maturation in the Sertoli cells.

****** The blood in the spermatic vessels flows in *a countercurrent system* (as in the loops of Henle in the kidneys). Such arrangement allows passage of testosterone *from the spermatic veins to the spermatic arteries* (which contributes in maintaining a high testosterone concentration in the testes).

(C) Other hormones : Estrogens and inhibin depress spermatogenesis by inhibiting FSH secretion. On the other hand, *thyroxine stimulates* spermatogenesis (page 39) , so it is depressed in cases of myxedema (page 44).

****** Administration of **exogenous androgens** in large doses inhibits LH secretion, so the secretion of endogenous androgen by the Leydig cells is decreased. This decreases the local androgen concentration in the testes resulting in depression of spermatogenesis, so treatment with exogenous androgens can be used as a method of *contraception in males* (page 128).

(2) TEMPERATURE

Spermatogenesis requires a lower temperature than that of the body (optimally 32-33 °C). Rise of the testicular temperature e.g. due to *cryptorchidism* (see below), fevers or continuous wearing of tight pants, damages the germinal epithelium (thus inhibiting spermatogenesis) and may kill any preformed sperms resulting in infertility (sterility). It also increases genetic mutations during cell division, which would produce *abnormal fetuses*. Therefore, for normal sperm formation, it is *essential for the testes (which develop in the abdominal cavity where the temperature is high) to descend to the inguinal canals (which depends on the MIS, page 105), then to the scrotum*, in which they are cooled by the following mechanisms :

- a. The scrotal skin is thin (as it contains little fat) and is rich in sweat glands. These favour heat loss (specially in presence of air currents).
- b. Heat loss is also favoured by the countercurrent system of the testicular vessels. It allows heat transfer from the spermatic arteries to the spermatic veins (which decreases the temperature in the scrotum).
- c. The scrotal muscle (= *Dartos muscle*) relaxes in hot weather, which draws the testes further away from the high temperature of the abdomen.

****** Spermatogenesis is **also depressed at lower temperatures than 32 °C**. For this reason, the dartos muscle contracts in cold weather to draw the testes upwards (in order to be warmed by the abdominal temperature).

Cryptorchidism (undescended testes)

This is a congenital abnormality in which **one or both testes fail to descend into the scrotum** (which normally occurs during the 7th - 8th month

Section II - Chapter 2

The male reproductive system

of pregnancy). The high abdominal temperature damages the germinal epithelium, so *azoospermia* (= *absence of sperms in semen*) may occur resulting in sterility. However, the **interstitial cells of Leydig are not affected by high temperatures**, so they secrete testosterone normally (thus the male secondary sex characteristics will appear normally at puberty).

Testicular descent occurs spontaneously in most cases. However, if it is delayed, it can be **induced by GTHs** (but if such treatment fails, **surgical interference** will be necessary). Treatment should be started before puberty **as early as possible** (a) To avoid excessive damage of the germ cells which is irreversible (b) Because the **undescended testes are more liable to malignant tumours**.

(3) DIET

A balanced diet containing adequate amounts of proteins and vitamins (specially vitamins A, E, C and B) is necessary for normal spermatogenesis. In prolonged starvation or malnutrition, spermatogenesis is depressed and may stop due to deficient secretion of the pituitary GTHs. Vitamin A deficiency causes keratinization and atrophy of the germinal epithelium, while vitamin E deficiency causes degeneration of the seminiferous tubules *in rats* (but this was not proved in humans). Vitamin C and the various members of vitamin B catalyze the metabolic processes in the germ cells (so their deficiency is also associated with depression of spermatogenesis).

(4) OTHER FACTORS

Prolonged exposure to various types of radiations (x-ray, atomic or nuclear radiations), prolonged hypoxia, certain toxins and infections (e.g. **mumps**) all damage the seminiferous tubules and depress spermatogenesis.

ENDOCRINE FUNCTION OF THE TESTES

The testes secrete **3 hormones** (testosterone, inhibin and estrogens).

Inhibin

Inhibin is a **polypeptide hormone** secreted by the **Sertoli cells in males and the granulosa cells of the ovarian follicles in females**. There are 2 types (A and B), and both **inhibit FSH secretion** by a direct negative feedback action on the anterior pituitary gland (specially type B). Such effect autoregulates the rate of FSH secretion and its blood level.

It can be used as a method of contraception in males (page 128) since it depresses spermatogenesis secondary to inhibition of FSH secretion.

****** From the inhibin precursors, other polypeptides that **stimulate FSH secretion** are also formed, and are called **activins** (however, their exact role in reproduction is unsettled). **Inhibins and activins are also found in the brain and many other tissues e.g. the placenta** (page 139). In the bone marrow, activins are involved in development of the white blood cells, and in embryonic life they are involved in the formation of mesoderm.

Estrogens in males

About 80-90 % of estrogens in the plasma of adult men is formed by **aromatization of the circulating testosterone & androstenedione** (probably in adipose tissue), and the remainder is secreted by the testes, *mainly by the Sertoli cells* (page 105) and a very small amount by the Leydig cells. The estrogen production in men is about 50 microgm / day (and it increases with advancing age) and its plasma level ranges from 20 to 50 pg/ml.

TESTOSTERONE

This is a C₁₉ steroid that is synthesized from **cholesterol**. In males, it is secreted mainly by the testicular interstitial cells of Leydig **under influence of LH** (at a rate of 4 - 9 mg /day) while in females, a very small amount is secreted from the ovaries. The adrenal cortex probably also secretes very small amounts in both sexes under influence of ACTH.

Androgens are **masculinizing hormones** (= hormones that produce male sex characteristics), and **testosterone is the most potent androgen**. The main androgens secreted by the adrenal cortex are **dehydroepiandrosterone (DHEA) and androstenedione**, and their potency is only about 20 % that of testosterone (page 58).

Mechanism of action of testosterone

Like other steroid hormones, testosterone binds to **cytoplasmic receptors** in the target cells, resulting in **increased transcription of mRNAs** which stimulate synthesis of proteins that alter the cell function (page 5).

Testosterone transport and concentration in the plasma

About **98 % of the plasma testosterone is bound to proteins** : 33 % to albumin and 65 % to a beta globulin called **gonadal steroid-binding globulin (GBG)**. The plasma testosterone level (free and bound) is about 300-1000 ng/dL in adult men (and it declines somewhat with age) and 30-70 ng/dL in adult women (dL = deci-litre = 1/10 litre = 100 ml or cm³).

Metabolism of testosterone

A small amount of testosterone is converted into estrogen (see above). However, most testosterone is converted into **17-ketosteroids** which are excreted in the urine. In males, about 1/3 of the urinary 17-ketosteroids are of testicular origin while the remaining 2/3 are of adrenal origin (page 51). Most 17-ketosteroids (but not all) are **weak androgens** (having only about 20 % of the potency of testosterone).

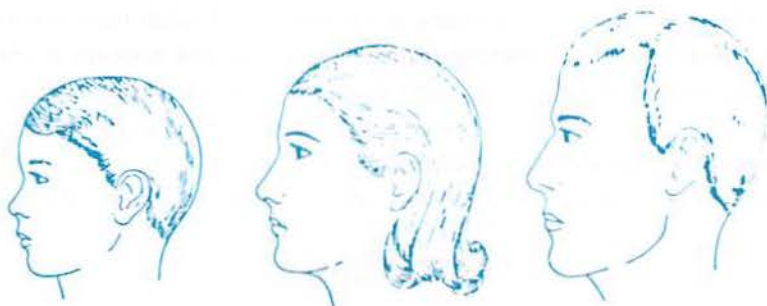


Figure 40 : Frontal scalp hairline in children and adult men and women.

ACTIONS OF TESTOSTERONE

- (1) Testosterone secreted during intrauterine life by the embryonic testes is responsible for maturation of the **wolffian ducts** that consequently develop into the **male internal genital organs** (page 99).
- (2) Testosterone is essential for **normal spermatogenesis** (page 106).
- (3) Appearance of male changes at puberty (**virilization**) which include :
 - A. Rapid growth of the **accessory sex organs** (page 103).
 - B. Appearance of the **secondary sex characteristics** which include :
 - a. **Hair growth** : The body hair increases particularly in the face (so the beard appears), chest, limbs, axillae and around the anus. The pubic hair grows in the form of a triangle with its apex up (= **male escutcheon**). However, the *scalp hair falls* with bilateral temporal recession of the frontal scalp hairline (figure 40), and *baldness is accelerated*.
 - b. **Changes in the quality of voice** : The larynx enlarges and the vocal cords increase in length and thickness (so *the voice becomes deeper*).
 - c. **Psychological changes** : At puberty, boys become aggressive and their interest in sex develops with increased libido (sexual desire).

d. Changes in body conformation : The shoulders broaden and the muscles enlarge due to the anabolic effect of testosterone (see below).

e. Skin changes : The secretion of the sebaceous glands increases and thickens (which predisposes to the development of **acne**).

(4) METABOLIC ACTIONS OF TESTOSTERONE

1. Anabolic action : Testosterone increases the synthesis and decreases the breakdown of protein, leading to an increase in the growth rate.

2. Moderate retention of Na^+ , K^+ , water, Ca^{2+} , SO_4^{2-} and PO_4^{3-} (secondary to the anabolic action) and an *increase in the size of the kidneys*.

3. Increase of both the iodide uptake by the thyroid gland and the secretion of the thyroid hormones which *increases the metabolic rate*.

4. Fusion of the epiphyses of the long bones to their shafts (which limits the initial spurt of growth that occurs at puberty).

5. Stimulation of secretion of the **erythropoietin hormone**, thus increasing the rate of red blood cell formation (refer to blood).

6. Insulin-like action (testosterone directly increases glucose uptake by the tissues and also their sensitivity to insulin).

Dihydrotestosterone (DHT)

Testosterone is converted to DHT in some target cells by activity of an enzyme called **5 alpha-reductase** (see below). The plasma level of DHT is about 10 % that of testosterone and it binds to the same receptors of testosterone. However, the *DHT - receptor complexes are more stable than the testosterone-receptor complexes*, thus *DHT formation is a way of amplification of the actions of testosterone*. This is required in the target tissues where it is formed (see next).

THE 5 ALPHA – REDUCTASE ENZYME & FUNCTIONS OF DHT

There are **2 types** of the 5 alpha-reductase enzyme. Type I is present in the skin throughout the body and is specially rich in the scalp, while type II is present in the genital skin and the prostate as well as in some other genital tissues. Consequently, DHT is formed in these tissues in considerable amounts, and performs the following functions (*rather than testosterone*) :

1. In the fetus, it induces development of the prostate and external genital organs (page 99).

2. At puberty, it causes **(a)** Enlargement of the prostate (and also the external genitalia i.e. penis and scrotum together with testosterone) **(b)** Hair growth all over the body specially facial hair **(c)** Fall of the scalp hair and bilateral temporal recession of the frontal scalp hairline **(d)** Increased secretion of the sebaceous glands and development of acne.

Section II - Chapter 2

The male reproductive system

****** Since DHT causes prostatic enlargement, *5 alpha-reductase inhibiting drugs (which decrease DHT synthesis) are now used in the treatment of benign prostatic hyperplasia.*

****** After identification of DHT actions, the main actions that are produced **directly by testosterone** are (a) Development of *the internal genitalia* in the fetus (page 100) (b) Enlargement of the external genitalia at puberty *with DHT* (c) Increase of the muscle and bone mass (d) Increase of libido.

5 ALPHA - REDUCTASE DEFICIENCY

Deficiency of the 5-alpha reductase enzyme is often due to congenital disorders. However, its effects usually appear at puberty and include (a) Less enlargement of the prostate and penis than normal (b) No or little hair growth on the body (c) Dense scalp hair without temporal recession of the frontal scalp hairline (d) Decreased secretion of the sebaceous glands.

In rare cases, type II of this enzyme is mutated and not acting. This leads to failure of development of the male external genitalia (*although there are testes and male internal genitalia*) and appearance of female external genitalia instead i.e. *male pseudohermaphroditism* (page 101), so the newly born baby is considered a female. However, at puberty and under the effect of LH, excessive amounts of testosterone are secreted from the testes which causes male body contours and male libido as well as marked enlargement of the clitoris like a penis. At this time, these individuals usually change their gender identities and become males.

ANDROGEN RESISTANCE

This is a condition in which testosterone is secreted from the testes, but it is unable to exert its effects due to either absent or abnormal androgen receptors, or inability to change to DHT due to *lack of the 5 alpha-reductase enzyme* (page 101). In mild cases, the male characteristics do not develop at puberty, and there will be infertility with or without gynecomastia (breast enlargement). However, complete loss of receptor function results in a condition called the **testicular feminizing (or complete androgen resistance) syndrome**, which is a type of *male pseudohermaphroditism*. In this syndrome, MIS is secreted by the embryonic testes with testosterone, so female internal genitalia do not develop but there will be female external genitalia due to lack of response to (or absence of) DHT (see above). The individual is thus considered a female (*but the vagina ends blindly due to absence of the female internal genitalia*). However, the condition is diagnosed when the individual complains lack of menstruation.

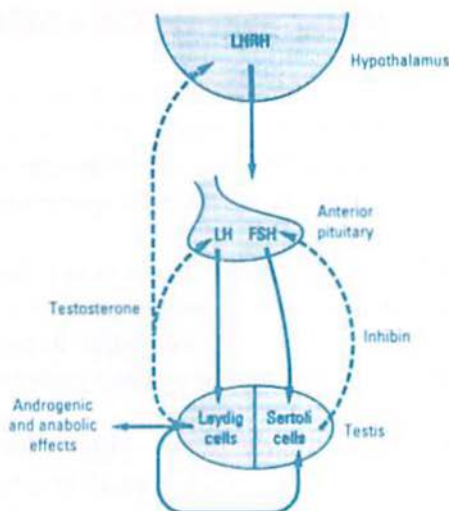


Figure 41 : Endocrine control of testicular function.

CONTROL OF TESTOSTERONE SECRETION

Testosterone is secreted by the embryonic testes and it induces development of the genital organs. It is secreted under effect of the **human chorionic gonadotropin hormone** which is secreted by the syncytiotrophoblast (page137) and **probably also by the fetal liver and kidney**. During the first year of life, there is a temporary increase in testosterone secretion, which is necessary for brain development, after which the testes remain quiescent till puberty. Maximum secretion of testosterone occurs at puberty under effect of LH, and is maintained afterwards till the age of **male climacteric** (which is about 60 years) after which it declines gradually.

In adults, the functions of the testes are normally **completely controlled by the GTHs (FSH and LH)**, the secretion of which is stimulated by the GnRH released from the hypothalamus (figure 41). Due to such hypothalamic control, testosterone secretion is altered in emotions and many psychological disorders. Its secretion also shows a **diurnal rhythm** (being highest during night at puberty, and in the early morning in adults).

LH is tropic to the interstitial cells of Leydig (stimulating testosterone secretion) while **FSH is tropic to the Sertoli cells** (stimulating secretion of inhibin and estrogens) and the hormonal blood levels control the activity of the pituitary hypothalamic axis by feedback mechanisms.

A high testosterone blood level feeds back to inhibit LH secretion at both the hypothalamic and pituitary levels (figure 41), and vice versa. On the other hand, a high inhibin blood level feeds back to inhibit FSH secretion from the anterior pituitary gland, and vice versa.

MALE HYPOGONADISM

This results from failure of testicular function, and it is **2 types** :

(A) **Primary hypogonadism** : This occurs as a **result of a testicular disease** and it may be *complete* (i.e. all testicular functions are lost) or *partial* (e.g. in cryptorchidism in which only spermatogenesis is lost).

(B) **Secondary hypogonadism** : This occurs due to either pituitary or hypothalamic disease (*Kallmann's syndrome*), and is *usually complete*.

The clinical picture in cases of **complete hypogonadism** depends on *whether the condition develops before or after puberty* :

(1) Pre-pubertal hypogonadism : This condition is called *eunuchoidism* since its manifestations (which appear in adulthood) are similar to those occurring in *eunuchs* (= *individuals subjected to bilateral castration during childhood*). In addition to *sterility*, it is characterized by :

1. Infantile sex organs and loss of libido (sexual desire).
2. A taller stature than normal (due to delayed fusion of the epiphyses to long bones) and may be a *greater span* (= distance between the full extended arms) than the body height (normally both are nearly equal).

3. *Absence of male secondary sex characteristics* : The body configuration resembles that of females (narrow shoulders, small muscles and feminine fat distribution in the hips and lower abdomen). The voice is high-pitched and the frontal scalp hairline does not recede. Pubic and axillary hair appear (by the adrenocortical androgens) but the hair is sparse, and in the pubic region, it is **triangular with the base up** (as in females).

(2) Post-pubertal hypogonadism : This condition occurs as a result of testicular, pituitary or hypothalamic disease. It also *normally occurs in old age* (and is called *male climacteric*) at about the age of 60 years (but it varies greatly, and there is *no andropause* similar to the menopause that occurs in women). It is characterized by the following :

1. Depressed sexual functions and libido, in addition to sterility.
2. Wasting and osteoporosis due to loss of the androgen anabolic effect.
3. The secondary sex characteristics and accessory sex organs are *almost not affected* (since they need very little androgen for maintenance), so the voice remains deep and the body hair and penis are not affected.

4. The patients occasionally have symptoms like those occurring in menopausal women (e.g. *hot flushes, sweating and palpitation*).

5. *Psychological disturbances* : The patients commonly become more irritable, passive and depressed.

The testicular function tests (fertility tests)

1. Measurement of the GTHs level in the urine : These are increased in primary hypogonadism and decreased in secondary hypogonadism (so this test is used to differentiate between the 2 conditions).

2. Estimation of the 17-ketosteroids level in the urine : These are decreased in testicular diseases since they are the main metabolites of testosterone (page 110). It is noted that the urinary excretion of the 17-ketosteroids is also altered in diseases of the adrenal cortex (page 65).

3. Testicular biopsy (= microscopic examination of a sample from the testis).

4. Semen analysis : Semen is the fluid ejaculated at **orgasm** (= end of intercourse). It contains the spermatozoa suspended in the *seminal plasma* (= secretions of the seminal vesicles, prostate and Cowper's glands).

NORMAL SEMEN

This is a whitish, opalescent, viscous and alkaline fluid (having a specific gravity 1028 and pH 7.35-7.5). Its normal average volume per ejaculate is **2.5 - 3.5 ml** and the normal count of sperms averages **100 million / ml** with **less than 20 % abnormal and immotile forms**.

The secretion of the seminal vesicles forms about 60 % of the total volume of semen, and it contains *fructose* (which is the main nutrient for the sperms), as well as flavins, ascorbic acid and prostaglandins.

The prostatic secretion is alkaline and forms about 30 % of the total volume of semen. It contains citric acid, calcium and acid phosphatase as well as *proteolytic enzymes and other elements*.

Causes of reduced male fertility

A sample of semen can be obtained by *prostatic massage* (manually through the rectum). The fertility power of semen is reduced when :

1. Its viscosity is abnormally high (which precludes the motility of the sperms in the female genital tract) .

2. Its volume per ejaculate is less than 2 ml.

3. Its sperm content is below normal (= **oligospermia**) or it contains no sperms at all (= **azoospermia**). A sperm count below 50 million / ml of semen is considered subfertile (50 % of men with sperm counts of 20 - 40 million / ml and all men having counts below 20 million / ml are sterile).

4. Its fructose content is greatly reduced.

5. Its content of abnormal or immotile sperms exceeds 25 %.

CHAPTER 3

THE FEMALE REPRODUCTIVE SYSTEM

The female organs of reproduction include the following (figure 42) :

(1) The ovaries (= female gonads) : These constitute *the primary sex organs in females*, and they perform the following functions :

- a. An exocrine function (production and extrusion of ova).
- b. An endocrine function (secretion of *estrogens, progesterone and inhibin, as well as relaxin and a small amount of testosterone*).

(2) The accessory (secondary) sex organs : These include :

a. **The vagina :** This is a distensible muscular tube that leads from the external genitalia (the vulva) to the uterus. The protruding part of the uterus into the upper part of the vagina is called the *uterine cervix*.

b. **The uterus** (the muscular organ in which the fetus develops).

c. **The 2 uterine tubes (fallopian tubes or oviducts) :** These are muscular tubes through which the ova discharged from the ovaries pass to the uterine cavity. At their ends, there are *fimbriae* which encroach upon the ovaries (facilitating entry of the ova into the uterine tubes).

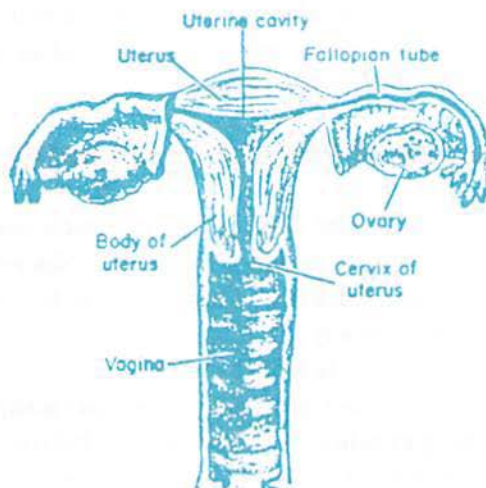


Figure 42 : The female reproductive system.

Gametogenic function of the ovary (= oogenesis)

Unlike spermatogenesis, the proliferation of the primitive germ cells in the ovaries (*the oogonia*) *occurs only during embryonic life, so no new ova are formed after birth*. The oogonia grow into **primary oocytes** each of which is surrounded by a single layer of flat epithelial cells called the **granulosa cells**, forming a **primordial follicle** (figure 43). At the 6th month of embryonic development, there are 7 million of these follicles in both ovaries, but many undergo **atresia** (= degeneration) *so that at the time of birth, there are only about one million normal follicles*. Meiosis starts in the primary oocytes but it is arrested in the prophase stage, and they *remain in this condition till puberty*. Follicular atresia then continues, so their **number in both ovaries at puberty becomes only about 300000**.

The ovarian functions start **at puberty** (average 12 years) and stop **at the menopause** (average 50 years). During the period between these 2 events (which is the **reproductive life span of the woman**), only one ovum (sometimes more) is discharged from the ovaries approximately every month (*probably alternately*). Therefore, during a normal female reproductive life span, only about **500 ova** are discharged from the ovaries (aiming to form a fetus) while the remaining ova degenerate.

Just before ovulation, **the meiotic division is completed** forming the **secondary oocyte** while the first polar body (figure 36) degenerates. Accordingly, **the released ovum is in the stage of secondary oocyte** and it immediately begins to divide, but such division stops at the metaphase and is **completed only when the ovum is fertilized**. At that time, the second polar body is expelled and the fertilized ovum proceeds to form a fetus.

THE SEX CYCLES IN FEMALES

These are regular cyclic changes that occur in the adult females specially in the reproductive system. They **start at puberty and continue till the menopause**, *stopping only during pregnancy or by disease*. The ovarian and uterine cycles constitute **periodic preparations for pregnancy**, and the latter is characterized by vaginal bleeding (= **menstruation or menses**).

The duration of a single cycle is not constant in all women, but on the average, it is **28 days from the start of one menstrual period to the start of the next**. *The first day of menses is considered as the first day of the cycle and the days of the cycle are identified by numbers starting from this day*.

The first event at puberty in girls is development of the breasts (= **thelarche**) followed by appearance of the axillary and pubic hair (= **pubarche**) then by menstruation (the first menses is called **menarche**).

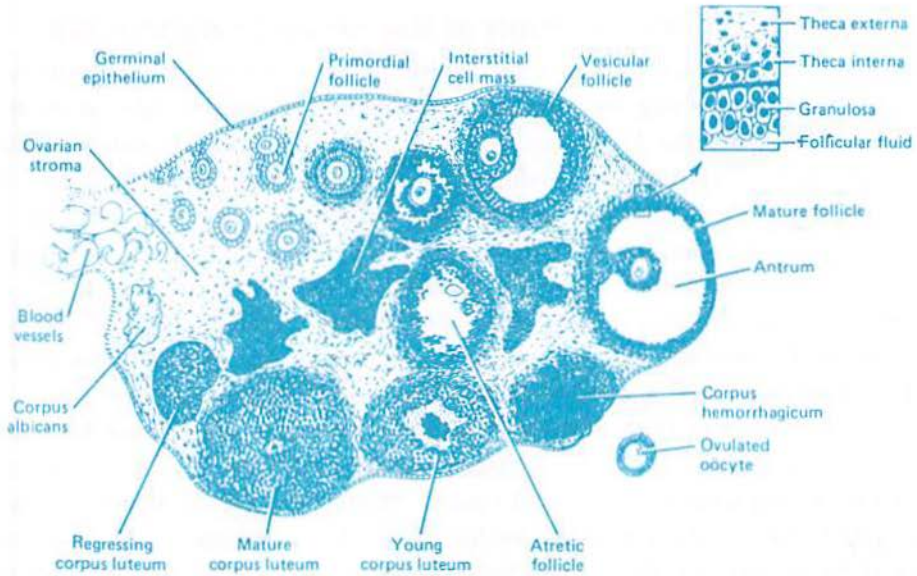


Figure 43 : Diagram of a mammalian ovary showing development of a graafian follicle and formation of the corpus luteum.

The ovarian cycle

The ovarian cycle consists of 3 phases : (1) Follicular phase (2) Ovulation phase (3) Luteal phase.

(1) The follicular phase

This phase starts with the first day of menstruation and ends with ovulation. Its duration is *not constant* due to variability of the time of ovulation. However, since ovulation often occurs in the 14th day of the cycle, this phase usually extends from the **first day to the 14th day of the cycle**.

Early in this phase, several primordial follicles (6-20) start to grow under influence of **FSH**, which acts on the granulosa cells (GCs) by binding to specific **FSH receptors** (so **FSH is responsible for the early growth of the follicles**). FSH causes hypertrophy and hyperplasia (= proliferation) of the GCs, and stimulates them to secrete (a) A fluid rich in protein, polysaccharides and electrolytes (= **follicular fluid or liquor folliculi**) into a cavity that forms around the ovum (= **antrum**), which gradually increases in size causing displacement of the ovum to one side of the follicle (b) An **estrogen (estradiol)** in the follicular fluid (c) A mucopolysaccharide substance called the **zona pellucida** which surrounds the ovum directly.

**** FSH stimulates synthesis (and secretion) of estradiol in the GCs by increasing the activity of the aromatase enzyme (which converts androgens into estrogens), and androgens are provided to the GCs cells from the theca interna cells.** In turn, estradiol induces follicular growth and maturation **by increasing the number of FSH receptors on the GCs** (which augments the growth promoting effects of FSH).

The growing follicles also acquire 2 layers from the ovarian stromal tissue that surround the GCs. These are (a) An inner richly-vascularized cellular layer called the **theca interna** (b) An outer poorly-vascularized fibrous layer called the **theca externa**.

On about the 6th day of the cycle, **only one follicle in one ovary starts to grow rapidly**, becoming a **dominant (or graafian) follicle** (figure 43) while the others become **atretic** (i.e. regress then degenerate). *The selection of the dominant follicle is related to the ability of its GCs to secrete estradiol, which is required for its maturation* (see above). The atresia of the other growing follicles occurs due to **insufficient FSH receptors in some follicles and inadequate secretion of estradiol in the others**.

Under influence of FSH, the mature GCs also acquire LH receptors. This is important because LH (a) Stimulates estradiol secretion by the GCs (so **both FSH and LH are responsible for the final maturation of the graafian follicle**) (b) Plays an essential role in the processes of **ovulation and formation of the corpus luteum** (see next).

(2) The ovulation phase

Ovulation *is the process of expulsion of the ovum from the graafian follicle*. It occurs in the **midcycle**, usually on the **14th day** (but it may occur slightly earlier or later than this day). The mature graafian follicle is pushed towards the periphery of the ovary and protrudes against its wall. It then ruptures, and the ovum (surrounded by the zona pellucida and a single layer of epithelial cells) is extruded into the abdominal cavity in the **secondary oocyte stage** (page 117) together with some follicular fluid. The ovum is then picked up by the fimbriated end of the fallopian tube and is transported to the uterus where it is fixed (if fertilized) or lost out through the vagina during menstruation.

Rupture of the graafian follicle occurs as **a result of a burst of LH secretion** called the **LH surge** (page 124). LH is thus **the hormone of ovulation**, and it produces this function by (a) **Increasing the secretion of the follicular fluid** which increases the intrafollicular pressure and compresses the ovum towards the follicular wall (b) Stimulating the follicular cells to secrete **proteolytic enzymes that break down the ovarian wall**.

(3) The luteal phase

The duration of this phase is remarkably **constant at 14 days**, usually from the **15th to the 28th days of the cycle**. The ruptured follicle is filled with blood forming a **corpus hemorrhagicum** (figure 43). The blood is gradually absorbed and the follicular cells hypertrophy and proliferate, and a yellowish lipid material appears in their cytoplasm. These cells are called the **luteal cells**, and within 1 to 2 days, the luteal cell mass develops into an endocrine organ called the **corpus luteum** (= **yellow body**). The formation of the corpus luteum **depends on LH** (page 124) as well as on development of an adequate blood supply, which is produced by a **vascular endothelial growth factor (VEGF)**.

Under influence of LH, the corpus luteum continues to grow and secrete hormones (estrogen and progesterone) for about 10 days, reaching full maturation on about the **24th day of the cycle**. If pregnancy occurs, it persists and grows further (and is called the **corpus luteum of pregnancy**) by the effect of a hormone called **human chorionic gonadotropin** (page 137).

On the other hand, if pregnancy does not occur, the corpus luteum (which is now called the **corpus luteum of menstruation**) begins to degenerate (= **luteolysis**) and within about 2 months, it is replaced by scar tissue forming a **corpus albicans** (= **white body**). The process of luteolysis is produced by the combined actions of (a) **Certain prostaglandins**, which may be formed by **locally-produced oxytocin from the corpus luteum** (page 31) (b) **ET-1** (= Endothelin -1).

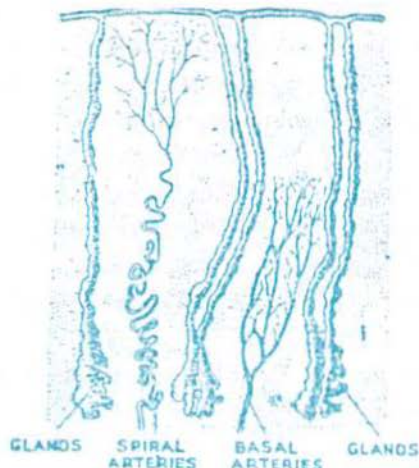


Figure 44 : Blood supply of the endometrium.

The uterine (or menstrual) cycle

This cycle occurs secondary to the ovarian cycle and consists of the cyclic changes that occur in the mucosal (inner) layer of the uterus called the **endometrium**. This layer is formed mainly of connective tissue stroma that contains tubular glands, and is divided into 2 main parts :

1. **A functional (superficial) part** : This is covered by a single layer of columnar epithelial cells and it forms about 2/3 of the endometrial thickness. It is supplied by *long coiled spiral arteries* (figure 44) and is *destroyed and sloughed (shed off) during menstruation*.
2. **A basal (deep) part** : This forms about 1/3 of the endometrial thickness and is supplied by *short straight basal arteries* (figure 44). *It is kept intact during menstruation then it regenerates the functional layer*.

Phases of the uterine cycle

The uterine cycle consists of 3 phases (1) Bleeding phase (2) Proliferative phase (3) Secretory phase.

(1) The bleeding phase (= destructive or menstrual phase)

This phase lasts **3-5 days**, and it *coincides with the first 3-5 days of the follicular phase of the ovarian cycle*. It occurs as follows : The corpus luteum of the preceding cycle starts to degenerate on about the **24th day of the cycle** (page 120), so the blood levels of both estradiol and progesterone are decreased. This leads to *shedding of the functional layer* of the endometrium and **menstruation occurs about 4 days later** as a result of **withdrawal of the hormonal support for the endometrium** (so this type of bleeding is called *withdrawal bleeding*).

The endometrium is thinned out and severe spasm and necrosis (= death) occur *in the walls of the spiral arteries*. This results in *ischemia and necrosis of the superficial layers of the endometrium together with spotty hemorrhages*. The latter coalesce leading to bleeding, and the blood together with the sloughed (shed out) necrosed endometrial tissue form the **menstrual flow**. *Vascular spasm* is produced by locally-formed **prostaglandins** from the cellular phospholipids by activity of the **lysosomal enzymes** (which are released from the necrotic cells).

The amount of blood loss during menstruation varies from slight spotting up to 80 ml (average **30 ml**) and 75 % of it is *arterial blood* while 25 % is *of venous origin*. Normally, this blood *does not clot* because it contains **fibrinolysin** (which is produced by the endometrial tissue).

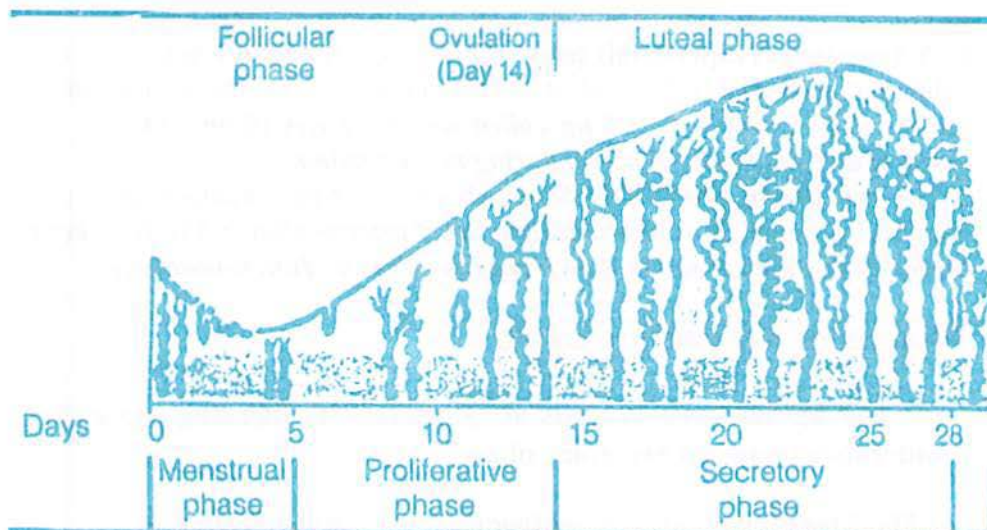


Figure 45 : Phases of the uterine (menstrual) cycle. The upper line shows the phases of the ovarian cycle.

(2) The proliferative (or preovulatory) phase

This phase starts after the end of menstruation and *it coincides with the follicular phase of the ovarian cycle except the first 3-5 days (during which menstruation occurs)*. Therefore, ***it terminates when ovulation occurs.***

Its duration averages **9 days**, but it is variable depending on the duration of the menstrual flow and the time of ovulation (*so variations in the length of the cycle are mostly due to changes in the duration of this phase*).

During this phase, the damaged superficial part of the endometrium after menstruation is regenerated from the basal layer. This occurs by the action of ***estradiol secreted by the theca interna cells of the graafian follicle (under influence of LH)*** as follows : **(a)** The deep pits of the endometrial glands (which remain intact after menstruation) start new epithelial growth which covers the inner surface of the uterus **(b)** The glands grow and increase in length but they do not secrete **(c)** The blood vessels grow and become spiral **(d)** The endometrium increases in thickness (becoming 3-4 mm thick) due to proliferation of its stromal cells.

(3) The secretory (or postovulatory) phase

This phase follows the proliferative phase and it *coincides with the luteal phase of the ovarian cycle, thus it starts after ovulation* and its duration is **remarkably constant at 14 days** after which menstruation occurs (in other words, *menstruation normally occurs almost exactly 14 days after ovulation*). During this phase, the endometrium is prepared for implantation of the ovum (if fertilized) *by the effect of estrogen and progesterone that are secreted by the corpus luteum* (particularly progesterone) through the following changes :

a. Further thickening of the endometrium (reaching about 6 mm thick), so it becomes *ready for implantation of the fertilized ovum*.

b. Deposition of large quantities of *fat, protein and glycogen* in the endometrial cells (which will be called *decidual cells* if pregnancy occurs).

c. *The endometrium becomes more vascularized* and the spiral arteries reach the endometrial surface.

d. *The endometrial glands become tortuous* (= coiled) and secrete a clear fluid, so the endometrium becomes *slightly edematous*.

FUNCTIONS OF LH : (1) *Final maturation of the graafian follicle* by stimulating (with FSH) estradiol secretion by the granulosa cells (page 119) (2) Stimulation of *estradiol secretion by the theca interna cells* which diffuses into the bloodstream and produces the *proliferative phase of the uterine cycle* (page 122) (3) *Ovulation, through the LH surge* (page 124) (4) Formation and maturation of the *corpus luteum* (124) (5) Stimulation of the corpus luteum to secrete progesterone and estrogen which produce the *secretory phase of the uterine cycle* (see above).

****** It is noted that *the bleeding and proliferative phases of the uterine cycle occur during the follicular phase of the ovarian cycle* while the *secretory phase occurs during the luteal phase of the ovarian cycle*.

HORMONAL REGULATION OF THE MENSTRUAL CYCLE

1. During the first 3-5 days of the follicular phase of the ovarian cycle (which coincides with the bleeding phase of the menstrual cycle), the blood levels of the ovarian hormones (estrogen and progesterone as well as inhibin) are low (figure 46). This stimulates secretion of the pituitary GTHs by a negative feedback mechanism. *FSH produces the early growth of the graafian follicle while both FSH and LH induce its final maturation* (page 119).

The theca interna has many LH receptors and *LH stimulates estradiol secretion from the theca interna cells (by converting cholesterol to androgen which is then converted to estradiol)*. Estradiol then diffuses into the bloodstream and **produces the proliferative phase of the uterine cycle** (page 122).

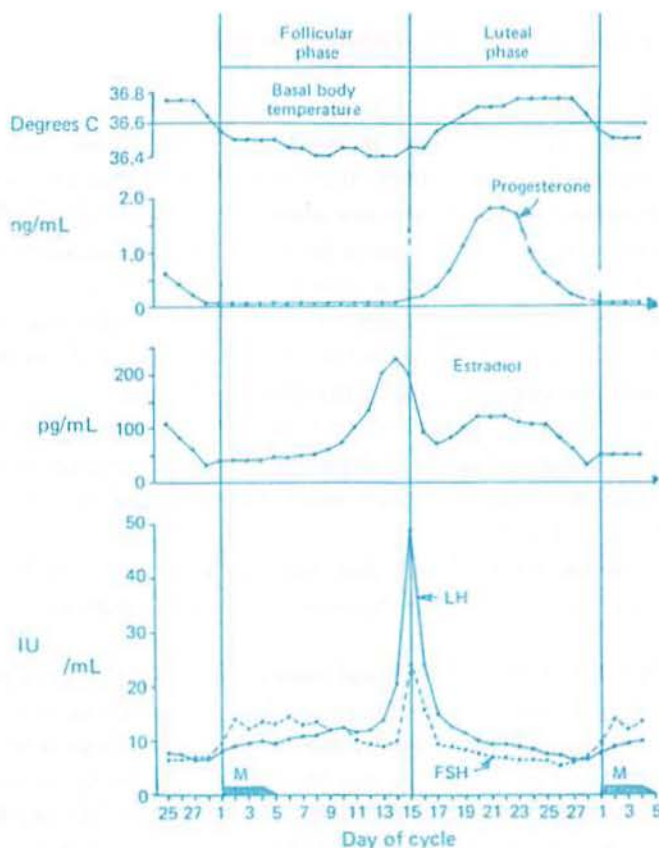


Figure 46 : The plasma concentrations of the ovarian hormones and GTHs (FSH and LH) during a normal menstrual cycle (M = menstruation).

2. The rising blood levels of estradiol (*secreted by the theca interna cells under effect of LH*) and inhibin (*secreted by the GCs under effect of FSH*) **limit the secretion of FSH by a negative feedback mechanism**. LH secretion is also held in check by the negative feedback effect of the rising plasma estradiol level. However, the blood FSH and LH levels remain high enough to maintain follicular growth and its secretory functions.

3. At about the 10th day of the cycle, the estradiol secreted by the theca interna cells is markedly increased, and at about the 12th day (i.e. 36-48 hours before ovulation) the excessively high blood estradiol level, **through a positive feedback mechanism, triggers a considerable burst of LH secretion called LH surge** (figure 46) **together with a smaller FSH surge** (in spite of the high blood level of inhibin). This effect of estradiol is attributed to augmentation of the responsiveness of the pituitary gonadotropes to GnRH. **LH induces ovulation about 9 hours after the LH peak then luteinization of the follicular cells, formation of the corpus luteum and its stimulation to secrete hormones (estrogen and progesterone).**

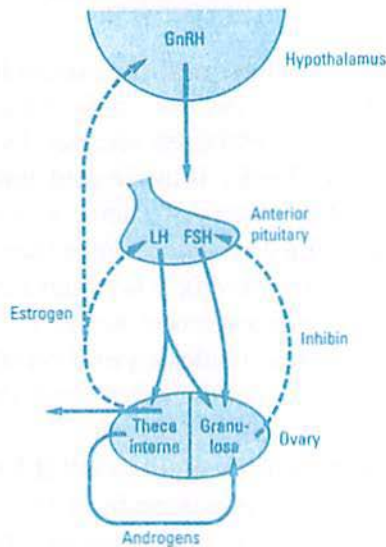


Figure 47 : Hormonal interaction in the control of ovarian functions. The dashed arrows indicate inhibitory effects.

4. After ovulation, the estrogen blood level temporarily drops, but however, it increases again together with progesterone, since they are secreted by the corpus luteum under effect of LH (figure 46). The blood levels of both hormones thus markedly increase, and they produce **the secretory phase of the uterine cycle, specially progesterone** (page 123).

5. The increased estrogen and progesterone blood levels inhibit secretion of the GTHs by a negative feedback action, so their blood levels decrease (figure 46). However, once the corpus luteum is formed, its activity is maintained independent of the GTHs for 10 days (till the 24th day of the cycle), after which luteolysis occurs. This is followed about 4 days later by **menstruation due to fall of the estrogen and progesterone blood levels after regression of the corpus luteum** (page 121).

6. The decreased estrogen and progesterone blood levels also lead to secretion of GTHs from the anterior pituitary by a negative feedback mechanism, which start a new cycle by inducing formation of a new graafian follicle.

**** The granulosa cells of the ovarian follicles are controlled by both FSH and LH.** The former stimulates secretion of **inhibin and estradiol** while the latter stimulates secretion of estradiol only, and **the secreted estradiol enters the follicular fluid**. On the other hand, the theca interna cells provide androgen to the GCs (to synthesize estradiol) and are controlled by LH only, which stimulates them to secrete estradiol that enters the circulation (figure 47).

Cyclic changes in the vagina and uterine cervix

The vaginal epithelium and the mucus in the uterine cervix undergo changes *secondary to the ovarian cycle* as follows :

(1) In the follicular phase, **estrogen** secreted by the graafian follicle makes the **cervical mucus elastic, thinner and more alkaline** (which promotes the survival and transport of sperms), and when spread on a slide, *it dries in an arborizing fern-like pattern* (fern is a feathery plant). On the other hand, the *vaginal epithelium becomes cornified*.

(2) In the luteal phase, **progesterone** secreted by the corpus luteum makes the cervical mucus **thick, tenacious and cellular** but it fails to form a fern-like pattern when dried. On the other hand, the *vaginal epithelium proliferates and is infiltrated with leukocytes*.

****** There are **other cyclic changes in adult females** which include :

1- The basal metabolic rate increases by 5-10 % and the basal body temperature rises by about 0.5 °C after ovulation (figure 46) due to the *thermogenic effect of progesterone* (page 133), and they remain high till the end of the cycle then they return back to their normal levels.

2- Under the effect of progesterone, the blood flow in the mammary glands increases. This leads to edema in the interstitial tissue of the breasts, so they swell and become tender and painful during the last 10 days of the cycle. However, such effects disappear with the onset of menstruation.

3- Under the effect of estrogen and progesterone (as well as aldosterone) some salt and water retention (and weight gain) occur in females during the few days that precede menstruation (= *premenstrual tension*). However, such effect disappears with the onset of menstruation.

4- Libido (sexual desire) is said to increase from the midcycle onwards (being highest towards the end of the cycle).

Reflex ovulation

Certain female animals ovulate *only after copulation*. This occurs reflexly through afferent impulses arising from the genitalia (in addition to visual, auditory and olfactory impulses) that converge on the hypothalamus (inducing release of GnRH, which produces ovulation by liberating LH from the anterior pituitary gland).

****** Reflex ovulation does not occur in human females. However, the menstrual cycle in women is frequently disturbed in the same way (i.e. through the hypothalamic control on the secretion of GnRH and GTHs) *e.g. during emotions and stressful conditions*.

ANOVULATORY (= NONOVULATORY) CYCLES

These are menstrual cycles **without ovulation**. They are normally common in the first 12-18 months after menarche, before the menopause and after stopping lactation (page 146). In these cycles, graafian follicles are formed and they secrete estradiol in amounts that produce endometrial growth but **fail to stimulate the LH surge**. Accordingly, ovulation does not occur, the corpus luteum is not formed and the secretory phase of the menstrual cycle disappears. However, estrogen continues stimulating proliferation of the endometrium, then sloughing and bleeding occur as a result of either regression of the graafian follicle (so sloughing occurs due to *estrogen withdrawal*), or *thickening of the endometrium* to the extent that induces its breakdown. The time it takes for bleeding to occur and its amount are variable in the anovulatory cycles. However, **the duration of these cycles is generally shorter than the duration of normal cycles (i.e. less than 28 days) in most cases.**

How can ovulation be detected ? (indicators of ovulation)

Ovulation can be detected by the following methods :

1. **Examination of an endometrial biopsy in the second half of the cycle :** The presence of features of the secretory phase indicates ovulation.
2. **Measurement of the basal body temperature** (in the morning before getting out of bed). Its rise by about 0.5 °C at about the middle of the cycle (in absence of disease) is indicative of ovulation (page 126).
3. **Examination of a vaginal smear and mucus from the uterine cervix :** The presence of the characteristic changes produced by progesterone (page 126) indicates ovulation.
4. **Estimation of the blood GTHs levels :** A sudden increase just before the midcycle (specially LH) suggests ovulation but is *not conclusive*.
5. **Estimation of progesterone level in the plasma (or pregnanediol in urine) :** Their increase in the second half of the cycle suggests ovulation.
6. **Observation of a fleeting lower abdominal pain at the middle of the cycle :** The presence of such pain (in absence of disease) often indicates ovulation. It is due to *peritoneal irritation* that occurs as a result of minor bleeding in the abdominal cavity after rupture of the graafian follicle.
7. **Observation of midcyclic bleeding :** This may occur due to drop in the blood estradiol level after rupture of the graafian follicle.
8. **Detection of ovarian thermal changes :** The ovarian temperature can be detected by a simple thermosensitive device. Its rise in one of the ovaries often indicates ovulation (such rise is due to hyperemia produced by the LH surge).

Contraception (prevention of pregnancy)**(A) Methods of contraception in females**

1- Contraceptive pills : Most contraceptive pills contain relatively large doses of both estrogen and progesterone or estrogen alone, which *inhibit the release of GTHs* by a negative feedback mechanism, thus preventing follicular growth and ovulation. Progesterone also makes the cervical mucus thick which precludes sperm migration.

****** Synthetic progesterone preparations (= **progestins**) alone (without estrogen) can also be used as contraceptives. They are available in the form of tablets, intramuscular injections (given once every 3 months) and as subcutaneous implants (which can prevent pregnancy for up to 5 years).

******: Large doses of estrogen taken by the woman after coitus for 4-6 days can prevent pregnancy by interference with implantation of the fertilized ovum. This is known as *postcoital (or morning after) contraception*.

2. Placing intra-uterine devices (IUDs) e.g. copper or plastic loops : These devices were thought to *interfere with ovum implantation* by disturbing the normal endometrial cyclic changes (which lead to failure of development of the progestational changes necessary for implantation). However, it is now believed that they **prevent sperms from fertilizing ova**. In addition, the devices that contain copper appear also to exert a spermatocidal effect.

3. Placing spermatocidal foams in the vagina : These foams either kill the sperms or preclude their motility (according to the type of foam).

4. Placing diaphragms in the vagina : These are intended to cover the uterine cervix, thus preventing the sperms from getting into the uterus.

5. Tubal ligation : This is ligation of the 2 fallopian tubes, so fertilization cannot occur. However, this method produces permanent sterility.

****** In lactating women, **breast feeding can be used as a method of contraception** because the lactation process prevents ovulation (page 146).

The rhythm method of contraception (Safe Period)

Since the ova are viable for fertilization for only about 24 hours after ovulation (although they may survive for 72 hours) and the sperms survive in the female genital tract for about 48 hours (and for longer times in some instances), the effective fertile period is about 72 hours (48 hours before and 24 hours after ovulation) and the *rhythm method of contraception depends on avoidance of intercourse at that period*. During the periods before the 9th day and after the 20th day of the cycle, there

is little chance for pregnancy to occur, and are thus called the **safe period**. However, this method is *not absolutely safe* because the time of ovulation is variable and some ova and sperms may survive for longer times than usual i.e. **no day in the cycle is quite safe**, and pregnancy was reported to occur *as a result of isolated coitus on every day of the cycle*.

(B) Methods of contraception in males

1. Coitus interruptus : This is rapid withdrawal of the penis just before ejaculation so that semen is ejected outside the female genital tract.

2. Taking a hot bath 30 minutes before coitus : This may be useful since heat depresses spermatogenesis and kills the stored sperms (page 107).

3. Use of condoms : Condoms are thin rubber sacs that are applied to the penis so that they tightly cover its glans. At the end of a sexual intercourse, the ejaculated semen will be collected in these sacs and thus prevented to enter the female genital tract.

4. Giving exogenous testosterone : Giving moderate daily doses of testosterone depresses spermatogenesis (page 107).

5. Giving GnRH-receptor blockers : These drugs inhibit the secretion of GTHs which suppresses spermatogenesis. **Inhibin** also decreases the secretion of FSH and is tried to be used as a contraceptive drug (page 108).

6. Vasectomy : This is bilateral ligation of the vas deferens. It is an efficient method of contraception, but it leaves the individual permanently sterile.

THE MENOPAUSE

Menopause is the cessation (stoppage) of the sex cycles in females. Menstruation usually becomes irregular then ceases between the ages of 45 and 55 years (commonly at **50-52 years**). This occurs due to (a) *Decline in the number of primordial follicles* (b) *Unresponsiveness of the ovaries to the GTHs*, although their secretion is increased by a negative feedback mechanism due to the decreased estrogen and progesterone blood levels. The decrease in the ovarian hormonal blood levels (specially estrogen) leads to the following changes :

- 1. Osteoporosis** (due to loss of the anabolic effect of estrogens).
- 2. Regression of the secondary sex characteristics.**
- 3. Atrophy of the accessory sex organs.**
- 4. Psychic manifestations** (irritability, anxiety, weakness, fatigue, headache, dizziness and may be true psychological depression).
- 5. Vasomotor disturbances :** There is commonly a sensation of hot flushes associated with sweating (probably due to an event that occurs in the hypothalamus). *These symptoms can be relieved by daily administration of small doses of estrogen.*

THE OVARIAN HORMONES

[A] ESTROGENS

These are C_{18} steroid hormones of which there are 3 types : **estradiol** (the most potent), **estrone** and **estriol** (the least potent). In females, estrogens in the circulation are secreted from (1) The ovaries (by the cells of the theca interna of the graafian follicles and the cells of the corpus luteum) (2) The placenta (page 139) (3) The adrenal cortex (very small amounts).

Plasma concentration and transport of estrogens

Only 2% of the circulating estradiol is free while the remainder is bound to protein, 60 % to albumin and 38 % to gonadal steroid-binding globulin (GBG).

The secretion of estrogens is continuous throughout the menstrual cycle, but it shows **2 peaks** (figure 46) :

1. **A maximal peak just before ovulation** (380 microgm / day) due to excessive secretion from the graafian follicle to initiate the **LH surge**.

2. **A smaller peak in the midluteal phase** (250 microgm / day) due to secretion from the corpus luteum.

Mechanism of action and metabolism of estrogens

Like other steroid hormones, estrogens act through increasing transcription of **mRNAs** in the target cells after binding to specific cytoplasmic receptors (page 6), then they are converted to glucuronide and sulphate conjugates in the liver, which are **excreted in the urine**. Some estrogens are also **excreted in the bile**.

ACTIONS OF ESTROGENS

Estrogens initiate and maintain all changes that occur in females at puberty. They also perform metabolic functions and special actions during pregnancy. These multiple actions are produced through their effects on :

- (1) **The primary sex organs (the ovaries)** : They induce growth and maturation of the graafian follicles, and are essential for formation of the corpus luteum by stimulating the **LH surge** (page 124).

- (2) **The accessory (secondary) sex organs** :

- a. **The uterus** : Estrogens stimulate growth of the myometrium and the endometrial epithelium and glands, and increase the uterine blood flow. They produce the **proliferative phase of the menstrual cycle**. They also increase the amount of uterine muscle in pregnancy, its activity and excitability and make the uterus **more sensitive to oxytocin** (page 142).

b. The oviducts (= uterine or Fallopoian tubes) : Estrogens stimulate growth of their mucosal and muscular layers and increase their motility.

c. The uterine cervix : Estrogens make the cervical mucus thin and alkaline which promotes the survival and transport of sperms (page 126).

d. The vagina : Estrogens cause thickening of the vaginal epithelial lining and cornification of its superficial layers (page 126).

e. The external genitalia : Estrogens are responsible for growth of the vestibular (= Bartholin's) glands and the vulva (the labia majora and minora).

(3) The female secondary sex characteristics : Estrogens are the *feminizing hormones* that produce the following changes in girls at puberty :

a. Changes in the body configuration e.g. narrow shoulders, broad hips, convergence of the thighs and divergence of the arms (*wide carrying angles*).

b. Characteristic fat distribution: Fat is deposited in the breasts, buttocks and lower abdomen (producing the characteristic feminine contours).

c. The larynx is *not* enlarged by estrogens, so the female's voice remains high-pitched as in children (due to absence of androgens).

d. Less body hair and more scalp hair without frontal recession. *Androgens from the adrenal cortex cause growth of the pubic & axillary hair.* The pubic hair is triangular with its base up (= *female escutcheon*).

(4) The mammary glands : Estrogens increase fat deposition and blood flow and maturation of the duct system leading to breast enlargement. They also induce growth of the nipples and darkening of the areolas. Such effects are intensified during pregnancy (page 144).

(5) Estrogens are also responsible for the *psychological and behavioural changes that occur in girls at puberty*. They also *increase libido* (= sexual desire) by a direct effect on certain neurons in the anterior hypothalamus.

(6) Interrelation between estrogens and other hormones :

a. The actions of estrogens on the endometrium and mammary glands are *necessary for progesterone to exert its actions*.

b. Estrogens control the secretion of GTHs as follows : A moderate constant increase in the plasma estrogen level inhibits secretion of the GTHs by a negative feedback effect, while a sudden increase in its plasma level stimulates secretion of GTHs by a positive feedback effect. The latter effect is manifested by the **LH and FSH surges** (page 124) and *is prevented if the plasma progesterone level is increased (as occurs in the luteal phase of the ovarian cycle)*.

c. Estrogens stimulate prolactin secretion during pregnancy *but prevent its milk secretory action by blocking its receptors in the breasts* (page 145).

d. Estrogens cause ACTH secretion and enlargement of the adrenal cortex.

e. Estrogens sensitize the myometrium to oxytocin action (page 142).

(7) Metabolic actions of estrogens :

- a. Estrogens exert a *protein anabolic effect* and *accelerate fusion of the epiphyses* (so the body stature is usually shorter in girls than in boys).
- b. Estrogens have a significant ***cholesterol-lowering action***. This may be the cause of the low incidence of atherosclerosis in women.
- c. Estrogens cause *salt and water retention*. This may cause *premenstrual tension* in some women before menstruation (page 126).
- d. Estrogens render the *secretion of the sebaceous glands more fluid, which prevents formation of blackheads (= comedones) and acne*.
- e. Estrogens increase the secretion of angiotensinogen by the liver.
- f. Estrogens increase the formation of the thyroid-binding globulin.

[B] PROGESTERONE

Progesterone is a C_{21} steroid hormone that is secreted mainly by the **corpus luteum and placenta**, and in very small amounts by the ovarian follicles (granulosa cells), the testes (Leydig cells) and adrenal cortex.

Plasma concentration and transport of progesterone

During the preovulatory (proliferative) phase of the menstrual cycle, the plasma progesterone level is about 0.9 ng /ml. Such value increases 20 fold (becoming 18 ng /ml) during the postovulatory (secretory) phase due to excessive secretion from the corpus luteum. Similar to estrogens, 2 % is free in the plasma while 98 % is bound to protein, 80 % to albumin and 18 % to the corticosteroid binding globulin (CBG).

Mechanism of action and metabolism of progesterone

Like other steroid hormones, the effects of progesterone on its target cells are produced by increasing *transcription of mRNAs* after binding to *specific cytoplasmic receptors, which are bound to a heat shock protein* (page 6). Progesterone is then converted in the liver mainly to *pregnanediol*, which is conjugated to glucuronic acid and excreted in the urine.

ACTIONS OF PROGESTERONE

Progesterone is essential for occurrence and maintenance of pregnancy (so it is the **hormone of pregnancy**). It performs the following actions :

(1) On the uterus

- a. It produces the *progestational changes in the endometrium* during the *secretory phase of the menstrual cycle* which are essential for embedding and implantation of the fertilized ovum and formation of the placenta.

b. It decreases the excitability of the myometrium (by increasing its resting membrane potential and decreasing its frequency of spontaneous electrical activity). It decreases the myometrial sensitivity to oxytocin (which is essential for the maintenance of pregnancy) and also the number of estrogen receptors in the endometrium.

(2) **On the uterine cervix and vagina :** Progesterone produces characteristic changes in the cervical mucus and vaginal epithelium during the luteal phase of the menstrual cycle (page 126).

(3) **On the mammary glands :** Progesterone stimulates development of the lobules and secretory alveoli of these glands, and full maturation occurs during pregnancy (page 145).

(4) **On the anterior pituitary gland & hypothalamus :** Progesterone inhibits LH secretion by a -ve feedback mechanism at both levels (and also potentiates the inhibitory effect of estrogen) so it prevents ovulation.

**** Accordingly, large doses of progesterone or one of the synthetic progestins are used as contraceptive drugs (page 128).**

(5) **On metabolism :**

a. Progesterone has *no significant anabolic effect*.

b. Large doses of progesterone produce *natriuresis* probably by blocking the action of aldosterone on the kidneys. It also causes *constipation*.

(6) **On body temperature :** Progesterone is *thermogenic* and it probably causes rise of the basal body temp. if ovulation occurs (page 126).

(7) **On respiration :** Progesterone stimulates respiration, leading to a decrease in the alveolar CO₂ tension in women during the luteal phase of the menstrual cycle as well as during pregnancy.

[C] RELAXIN

This is a *polypeptide hormone* (which structurally resembles the human insulin and IGFs). During pregnancy, it is markedly secreted in the first trimester by the *placenta and the corpus luteum of pregnancy under effect of hCG (page 137)*, and it is also found in the mammary glands. It *relaxes the symphysis pubis and other pelvic joints*, and *softens and dilates the uterine cervix*, thus facilitating delivery. It also *inhibits uterine contractions* and may help development of the *mammary gland*. In non-pregnant women, it is found in the *corpus luteum and endometrium* (during the secretory phase) but its functions are unknown. *In men, relaxin is produced by the prostate gland and is found in the semen* (in which it may play a role in maintaining the sperm's motility and its ability to penetrate the ovum).

CONTROL OF SECRETION OF THE OVARIAN HORMONES

The secretion of the ovarian hormones is controlled primarily by the **hypothalamic-pituitary axis** (figure 47). The hypothalamus secretes the GnRH which stimulates secretion of the GTHs (FSH and LH) from the anterior pituitary gland, and these in turn control secretion of the ovarian hormones. *The GnRH is normally secreted in episodic bursts* the frequency of which (and consequently the rate of secretion of the GTHs) is adjusted by the blood levels of the ovarian hormones through the following **feedback mechanisms** :

1- FSH stimulates the granulosa cells to secrete **inhibin** which inhibits secretion of FSH from the anterior pituitary by a negative feedback action.

2- LH stimulates synthesis of estrogen *in the theca interna cells* from androgens (specially androstenedione), which is then secreted into the blood stream and produces the proliferative phase of the uterine cycle (page 122). Accordingly, the estrogen blood level moderately increases and this inhibits secretion of the GTHs by a negative feedback mechanism particularly at the pituitary level. *The theca interna cells also provide androgens to the granulosa cells for synthesis of estrogen that diffuses into the follicular fluid.*

3- When the estrogen blood level is excessively increased late in the follicular phase of the ovarian cycle, it stimulates secretion of GTHs by a **positive feedback action (LH and FSH surges, page 124)**. This effect occurs because the high estrogen blood level *increases the frequency of the GnRH bursts and the responsiveness of the gonadotropes to this hormone.*

4- LH stimulates the *mature granulosa cells* to secrete estrogen which is *important for full maturation of the graafian follicle with FSH* (page 119). LH also *induces ovulation* and formation of the corpus luteum after ovulation, and its stimulation to secrete progesterone and estrogen (page 124).

5- The increased progesterone blood level (potentiated by estrogen) inhibits the release of LH by a negative feedback mechanism (particularly at the hypothalamic level by decreasing the frequency of the GnRH bursts) which results in reduction of the blood levels of these hormones.

6- During the first 6-8 weeks of pregnancy, a special hormone called **human chorionic gonadotropin (hCG)** stimulates the corpus luteum to secrete estrogen and progesterone (page 137).

Abnormalities of ovarian function

These occur as a result of either ovarian disorders, or hypothalamic or pituitary diseases. The commonest abnormalities include the following :

(1) Anovulatory cycles (page 127) **(2) Menstrual abnormalities** (see next).

a. **Amenorrhea** (= absence of menstruation) : This may be **primary** (if the menstruation has never occurred) or **secondary** (if it occurs in a woman with previously normal periods). The latter may be due to disease or **normally during pregnancy** (page 141).

b. **Oligomenorrhea** : This is scanty (little) menstrual flow.

c. **Menorrhagia** : This is profuse (excess) menstrual flow.

d. **Metrorrhagia** : This is uterine bleeding between the periods.

(3) Hypo-ovarianism (female hypogonadism)

The manifestations of this condition *depend on the age of onset* :

a. **Before puberty** [e.g. due to congenital absence or mal-development of the ovaries), there will be **primary amenorrhea**, **sterility**, no develop-ment of the secondary sex characteristics, and the accessory sex organs remain infantile. In addition, the patient is **taller than normal** due to delayed fusion of the epiphyses to the long bones.

b. **After puberty** (e.g. due to a severe ovarian disease), there will be **secondary amenorrhea**, **sterility**, **regression of the sex organs**, **wasting**, **osteoporosis**, and the pubic hair decreases and becomes thinner. It is noted that such manifestations *occur normally after the menopause* (page 129).

(4) Ovarian tumours

The ovarian tumours are generally rare. Androgen-secreting tumours can cause *masculinization*, while estrogen-secreting tumours can cause (a) **Precocious sexual development** if they occur during childhood (b) **Irregular uterine bleeding** if they occur in adult life. *Uterine bleeding after the menopause is often the first indication of an ovarian tumour.*

PREGNANCY (GESTATION OR CONCEPTION)

FERTILIZATION AND IMPLANTATION

****** When ovulation occurs, the ovum is expelled into the peritoneal cavity then it enters the fimbriated end of the uterine tube, and fertilization usually takes place *in the lateral part (ampulla) of this tube.*

****** Sperms require a few hours in the female genital tract in order to become more capable for fertilization (= **sperm capacitation**, page 106) and fertilization is favoured by *chemo-attraction of the sperm to the ovum* by substances produced by the ovum.

****** Although millions of sperms are deposited in the vagina at the end of intercourse, only 50 - 100 reach the ovum, and only about 10 of these adhere to the zona pellucida (ZP) at *specific sperm receptors called ZP3*. This is followed by the **acrosomal reaction** i.e. breakdown of the acrosome at the sperm head (page 106) and release of various enzymes including a *trypsin-like protease called acrosin* which facilitates penetration of the sperm through the ZP.

****** After penetration of the ZP, the sperm head adheres to the cell membrane of the ovum. This is followed by breakdown of the area of fusion and release of the sperm nucleus into the cytoplasm of the ovum. Fusion of the sperm to the ovum membrane is mediated by **fertilin** (protein on the surface of the sperm head). The fusion causes reduction in the membrane potential of the ovum followed by a structural change in the ZP, and these events *prevent polyspermy* (= *penetration of the ovum by more than one sperm*) which leads to failure of fertilization.

****** The fusion of the sperm to the ovum provides the signal that initiates development. The result of such fusion is the **zygote**, which after about 1 day, starts to divide mitotically to form a **morula**. This moves slowly down the uterine tube (by the movement of cilia and also peristaltic contractions) and *reaches the uterus within 3-4 days after fertilization*.

****** The morula then develops into a **blastocyst**, which becomes surrounded by the **trophoblast** (which consists of **2 layers** : *an outer layer called syncytio-trophoblast and an inner layer called cytotrophoblast*). *On about the 6th day after fertilization, the ZP disappears and the trophoblast adheres to the endometrium.*

****** The process of implantation starts on the 6th - 7th day after fertilization and is completed on the 8th - 9th day. The syncytio-trophoblast erodes the endometrium and the blastocyst burrows into it till it becomes implanted. This usually occurs at the *posterior or dorsal wall of the uterus* (figure 48), and is followed by development of the placenta.

****** It is noted that implantation of the ovum starts about 1 week after its fertilization. *This delay is important because the endometrium is prepared during this period for implantation by the hormones of the corpus luteum.*

The corpus luteum of pregnancy

Progesterone is essential to maintain pregnancy (so it should be available throughout pregnancy) because it *reduces the excitability of the uterine muscle to oxytocin* (thus uterine contractions and abortion are prevented).

In ordinary (nonfertile) menstrual cycles, the increased blood levels of estrogen and progesterone secreted by the corpus luteum inhibit GTHs secretion and the corpus luteum degenerates on about the 24th day of the cycle (page 120).

However, if fertilization of the ovum occurs, the corpus luteum does not degenerate but, instead, it markedly enlarges and is called the **corpus luteum of pregnancy** (page 120). Such enlargement, in spite of inhibition of secretion of the pituitary GTHs, is caused by a hormone called the **human chorionic gonadotropin (hCG) or the placental gonadotropin** (see next page).

Human chorionic gonadotropin (hCG)

This is a glycoprotein secreted by the syncytiotrophoblast then the chorionic villi of the placenta (hence the name). It is *primarily luteinizing and luteotropic (like the pituitary LH) i.e. it induces growth of the corpus luteum and stimulates it to secrete estrogen, progesterone and relaxin for the first 6-8 weeks of pregnancy (therefore, ovariectomy before the 6th week of pregnancy leads to abortion)*. The secretion of hCG is *not subjected to a negative feedback inhibition* by the high plasma levels of estrogen and progesterone, but *after about the 8th week of pregnancy, its secretory rate progressively decreases (reaching a very low level by the end of the first trimester), causing regression of the corpus luteum*. However, secretion of estrogen and progesterone will be maintained from the placenta till the end of pregnancy (page 139). **hCG also exerts a TSH activity (page 40), and in a male fetus, it stimulates testosterone secretion by the Leydig cells of the embryonic testes (pages 99 and 113).** In addition, it probably participates in **development of the breasts during pregnancy (page 145).**

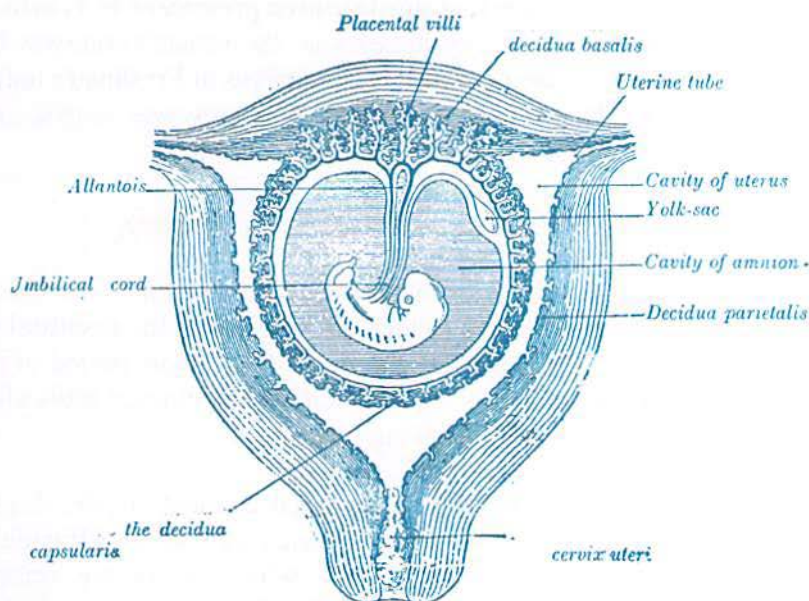


Figure 48 : The placenta and fetal membranes.

EARLY PREGNANCY TESTS

Pregnancy is suspected when amenorrhea occurs in a normal married woman. In this case, early diagnosis of pregnancy can be achieved by detection of hCG in either the blood or urine of the woman since this hormone is secreted by the developing embryo (the syncytio-trophoblast of the blastocyst). However, the detection of hCG *does not always indicate pregnancy because it is also secreted by certain tumours*. hCG can be detected *in the woman's blood as early as 6 days after conception* and in her urine *14 days after conception*. hCG can be measured by radioimmunoassay. However, the following tests for the early diagnosis of pregnancy can also be used, and they **depend on detection of hCG in the woman's urine** :

1- Immunological tests : These tests depend on *the interaction between hCG (as an antigen) and its antibodies*. In the **agglutination test** (the commonest used immunological test), the woman's urine is mixed with a solution that contains *granules of certain substances (e.g. latex) coated with hCG antibodies*. Agglutination of the substance indicates pregnancy, and vice versa.

2- Chemical tests : The woman's urine is added to a solution of an *indicator substance that changes its colour on contacting hCG*. Thus a change in the colour of the substance after addition of urine indicates pregnancy and vice versa.

****** These tests are *useful only in the first trimester of pregnancy*, since the hCG concentration in urine decreases to very low levels after this period.

****** In the past, **animal tests that also depend on presence of hCG in the urine** were used for the early detection of pregnancy. In these tests, **the woman's urine was injected into an animal** (e.g. mice in **Aschiem-Zondek test** and rabbits in **Friedman's test**), and after a certain period, the animal's ovaries were examined. Pregnancy was diagnosed if there were signs of ovulation and corpus luteum formation, and vice versa.

FUNCTIONS OF THE PLACENTA

After implantation of the fertilized ovum, the placenta is formed from the trophoblast and endometrial cells (which are now called the **decidual cells**, page 123). Its size increases progressively throughout the whole period of pregnancy, although it becomes functionally efficient for the developing fetus after about 8 weeks through performing the following functions :

(1) Nutritional function

The placenta supplies all nutritional elements to the fetus from the maternal blood. Some elements are transported by simple diffusion (e.g. fatty acids, most vitamins, Na^+ and K^+ salts) while others are transported by facilitated diffusion (e.g. glucose) and still others are transported by active transport (e.g. amino acids, Ca^{2+} , PO_4^{2-} and Mg^{2+} salts).

(2) Respiratory function

The placenta acts as a **fetal lung**. Fetal deoxygenated blood enters the chorionic villi via branches of the umbilical arteries where gas exchange occurs (CO_2 is eliminated to the maternal blood and O_2 diffuses from the maternal to the fetal blood) then the **umbilical vein carries oxygenated blood to the fetus**. O_2 delivery to the fetus is favoured by the high difference in PO_2 between the maternal and fetal blood, the high concentration of fetal hemoglobin (Hb F) as well as its high affinity to O_2 specially after unloading CO_2 (which causes shift of the O_2 dissociation curve to the left).

(3) Storage function

Early in pregnancy, considerable amounts of glycogen, protein and some elements (e.g. calcium and iron) are stored in the placenta to be used later by the growing fetus.

(4) Excretory function

In the placenta, the fetal metabolic waste products (e.g. urea, and creatinine) are excreted into the maternal blood by passive diffusion.

(5) Protective function

The placenta is an **efficient barrier** against passage of most bacteria and toxins from the maternal blood to the fetus. It is also **permeable to most antitoxins and antibodies** (particularly immunoglobulin G). On the other hand, most viruses and drugs can cross the placenta. For this reason, viral infections and most drugs **should be avoided during pregnancy (specially in the first trimester)** since certain viruses (e.g. those producing **german measles**) and some drugs may cause serious fetal malformations.

(6) Endocrine function

The placenta secretes the following hormones :

1. Human chorionic gonadotropin (hCG) : See page 137.

2. Relaxin : See page 133.

3. Estrogens : These promote (a) Enlargement of the uterus and increase of its blood supply (b) Growth of the mammary glands and development of their duct system (c) Enlargement of the external genitalia (d) Relaxation of the pelvic ligaments and joints (**like relaxin**) (e) Sensitization of the myometrium to the action of oxytocin. Their secretion markedly increases near full term, and through their actions on the myometrium and pelvic joints, they **facilitate delivery of the baby**.

Estrogens are synthesized through *an interaction between the placenta and fetal adrenal glands, which is known as the fetoplacental unit* (page 141), and the *main secreted estrogen is estriol*.

4. Progesterone : This is essential for maintenance of pregnancy by (a) Maintaining and increasing the progestational changes in the endometrium (b) Decreasing the sensitivity of the myometrium to oxytocin (thus preventing uterine contractions that would lead to abortion). It also promotes maturation of

the mammary glands and development of their secretory alveoli. In addition, the high blood levels of both progesterone and estrogen during pregnancy inhibit GTHs secretion from the anterior pituitary gland by a negative feedback action (thus *preventing the ovarian cycle and menstruation during pregnancy*). After regression of the corpus luteum of pregnancy on the 6th - 8th week (page 137), the placenta becomes the only source of estrogens, progesterone and relaxin.

5. Human chorionic somatomammotropin (hCS) : This is a protein hormone that is secreted by the *syncytiotrophoblast* (like hCG). It is also called *chorionic growth hormone-prolactin (CGP)* and *human placental lactogen (hPL)* because it exerts (a) Mammotropin (prolactin)-like action i.e. it stimulates milk secretion from the mammary glands (b) Somatotropin-like action i.e. it exerts most actions of *somatotropin (the pituitary growth hormone)* but *less efficiently* e.g. retention of the elements required for growth, increasing lipolysis and antagonizing insulin action (which increases the blood glucose level thus providing more glucose to the fetus). The amount of hCS in the maternal blood is *proportionate to the size of placenta* (which normally weighs about 1/6 of the fetal weight), and its decrease is a sign of placental insufficiency.

6. Other placental hormones : These include a growth promoting factor called *variant growth hormone*, *hC thyrotropin* (page 41), **CRH**, **MSH**, **Leptin** (page 94), *B-endorphin* and *pro-renin*. Variant forms of **prolactin** as well as **GnRH** and **inhibin** are also secreted. The latter 2 act locally for regulation of hCG secretion (GnRH increases while inhibin decreases hCG secretion).

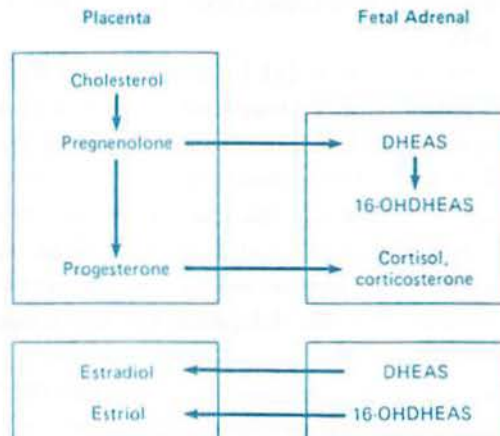


Figure 49 : The fetoplacental unit.

THE FETOPLACENTAL UNIT

This term refers to the interaction between the placenta and fetal adrenal cortex in the production of the placental estrogens as well as some adrenal corticosteroids. Such interaction occurs as follows (figure 49) :

- 1- The placenta synthesizes pregnenolone and progesterone from cholesterol
- 2- Some progesterone enters the fetal circulation and on reaching the fetal adrenal glands, it leads to formation of cortisol and corticosterone.
- 3- Some pregnenolone enters the fetal circulation and, with pregnenolone synthesized by the fetal liver, they lead to formation of both dehydroepiandrosterone sulphate (**DHEAS**) and 16-hydroxy-dehydroepiandrosterone sulphate (**16-OH-DHEAS**) in the fetal adrenal cortex.
4. Both DHEAS and 16-OH-DHEAS are then transported back to the placenta in which *the former forms estradiol while the later forms estriol.*

****** Since the *main estrogen formed is estriol* (see above), the urinary estriol excretion of the mother can be taken as an index of the fetal state (it should increase steadily throughout pregnancy if the fetal growth was normal).

Manifestations of normal pregnancy

- 1- **Amenorrhea (the first sign)** occurs due to feedback inhibition of release of the pituitary GTHs by the high blood levels of estrogen and progesterone.
- 2- **Morning sickness (malaise&vomiting)** often occurs in the first trimester, probably due to oversecretion of thyroxine by the hCG and hC thyrotropin.
- 3- **Acromegalic appearance of the face** (probably by the effect of hCS).
- 4- **Enlargement of internal and external sex organs and the breasts.**
- 5- **Increase of the basal metabolic rate** (due to excessive secretion of thyroxine and glucocorticoids, and the high blood levels of the sex hormones).
- 6- **Increase in the blood volume, venous return and cardiac output.**
- 7- **Mild increase in the urine volume and frequency of micturition.**
- 8- **The immune system may be inhibited** which decreases the body resistance against infections.
- 9- **Ankle edema of a varying severity** often occurs late in pregnancy due to obstruction of blood flow from the lower limbs by the enlarged uterus.
- 10- **Weight gain** (due to weight of fetus, its membranes, the amniotic fluid, the placenta, the enlarged uterus & breasts and the increased blood volume).
- 11- **Increase of the appetite and food intake** (which supplies the increased nutritional demand of the pregnant woman for her growing fetus).
- 12- **Increased pulmonary ventilation**, which supplies extra O₂ that is needed by the fetus and the mother (because of the increased metabolic rate).

13- Endocrinal changes

(a) **The anterior pituitary gland is enlarged** and secretes more **ACTH** probably by effect of the placental CRH (page 140). **Prolactin** secretion is also progressively increased during pregnancy by the effect of estrogen. However, *the secretion of some hormones is inhibited by a feedback action including GTHs* (by the increased blood levels of both estrogen and progesterone), the **growth hormone** (by the effect of hCS which is called the *maternal growth hormone of pregnancy*) and frequently also **TSH** (by the effect of hCG and hC thyrotropin).

(b) **The adrenal cortex secretes excessive amounts of glucocorticoids** (which increases the levels of amino acids, glucose and fatty acids in the maternal blood, thus promoting their supply to the fetus) and **aldosterone** (which leads to sodium and water retention in the mother's body).

(c) **The parathyroid glands are enlarged and secrete more parathormone specially if the mother's diet was poor in calcium.** The hormone mobilizes calcium from the mother's bones which is then delivered to the fetus.

(d) **The thyroid gland secretes more thyroid hormones under effect of hCG & hC thyrotropin** (which increase the metabolic rate) and also **calcitonin** (page 80) which limits Ca^{2+} mobilization from the mother's bones.

PARTURITION (DELIVERY OR LABOR)

The duration of normal pregnancy in humans **averages 270 days from the date of fertilization** (about 38 weeks). However, it is usually counted from **the first day of the last menstrual cycle**. From this day, the normal duration of pregnancy is therefore about **284 days** (which roughly equals about 40 weeks, 10 lunar months or 9 calendar months). During pregnancy, there are irregular episodic uterine contractions which are probably produced by the circulating oxytocin. However, at full term (= end of pregnancy) the delivery of the baby occurs by the following mechanism :

(1) As a preparation for labor in the last month, the frequency and strength of uterine contractions markedly increase as a result of 2 factors :

(A) Increased synthesis of estrogens from DHEAS (see above) with **marked increase in their blood levels**. Estrogens increase (a) The myometrial excitability and its sensitivity to oxytocin (pages 130 and 131) (b) **The number of oxytocin receptors** in both the myometrium and the decidua (= *endometrium of pregnancy*), which increase more than 100 fold during early labor (c) The formation of **certain prostaglandins which stimulate uterine contractions**. The first 2 effects of estrogens cause the myometrium to respond to the normal circulating oxytocin blood level (25 pg/ml) as well as to the **locally-produced oxytocin in the uterus** (page 31).

(B) **Uterine distension** : The distended uterus *increases the number of oxytocin receptors (together with estrogen)* and may also evoke *spinal reflexes* that cause contraction of the myometrium.

****** It was believed that the progesterone blood level drops in early labor together with the rise in the estrogen blood level. However, this does not occur in primates (thus the increase in the *estrogen-progesterone ratio* that occurs in early labor is *due mainly to the increased estrogen blood level*).

(2) **At full term**, the uterine contractions become stronger, more frequent, spasmodic and painful (so they are called *labor pains*). The uterine cervix is softened and dilated by the effects of *relaxin, estrogen and uterine contractions*. Such contractions push the baby down resulting in *stretch of the cervix*. This initiates reflex release of oxytocin from the neurohypophysis, which potentiates the uterine contractions, *denoting the onset of labor*.

(3) **Once labor starts**, it proceeds by **positive feedback cycles** that lead to progressively stronger uterine contractions as follows : As the baby is forced down, it leads to stretch of the uterine cervix and distension of the vagina. This sets up signals in afferent nerves that are transmitted via ascending tracts in the spinal cord to the hypothalamus, which stimulates oxytocin secretion from the neurohypophysis. Accordingly, the plasma oxytocin level rises and leads to more stronger uterine contractions which push the baby further down, resulting in more stretch of the birth canal, and *a positive feedback loop is thus established* which results in delivery of the baby (figure 50). *Oxytocin causes uterine contractions by a direct effect on the myometrium and by forming prostaglandins which directly cause uterine contractions and also enhance the oxytocin-induced contractions.*

****** During labor, reflex and voluntary contraction of the abdominal muscles (*bearing down*) also aid delivery. However, these actions (as well as reflex stimulation of oxytocin secretion) are *not essential for labor*, since paraplegic women (in whom the spinal cord is sectioned) can still deliver.

(3) **The process of labor is terminated by delivery of the baby**. The positive feedback cycles stop because the birth canal becomes no longer stretched. However, weak uterine contractions often continue spontaneously after delivery of the baby, and these (aided by external massage to the uterus) usually lead after 10-45 minutes to expulsion of the placenta and other products of conception. Placental separation from the uterine wall leads to rupture of most uterine blood vessels. However, the resulting bleeding normally stops rapidly (so that the dangerous **postpartum hemorrhage would be prevented**) because (a) The contracting uterine muscle fibres compress the blood vessels (b) V.C. occurs by effect of certain prostaglandins that are released at the time of placental separation

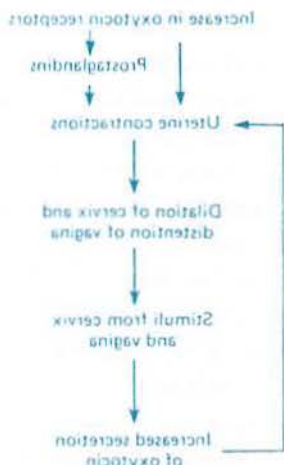


Figure 50 : Role of oxytocin in parturition.

****** The uterine contractions are essential for delivery and also prevent postpartum hemorrhage. However, if they are excessive or prolonged (e.g. when giving oxytocin for induction of labor) they become dangerous, since they *may occlude the placental blood vessels* to the extent that leads to placental ischemia and death of the fetus.

****** After delivery, the uterus involutes gradually, reaching its pre-pregnancy weight after about 5 weeks, and ***breast feeding hastens involution*** because it stimulates prolactin secretion, which inhibits the release of GnRH and GTHs as well as the effects of the latter on the ovaries (page 146).

THE MAMMARY GLANDS AND LACTATION

The mammary glands are modified sweat glands that develop at puberty. During childhood, the mammary glands are rudimentary (consisting of a few ducts lined with flat epithelial cells surrounded by a small amount of connective tissue). ***Their development & growth are controlled by the following hormones***

(1) Estrogens : These induce development of the mammary glands at puberty and also produce all its manifestations (page 131). Other hormones are also necessary *as permissive factors* for mammary development, namely ***glucocorticoids, insulin, growth hormone and prolactin***. During pregnancy, estrogens cause **(a)** deposition of more fat in the breasts (so they are markedly enlarged) **(b)** enlargement of the nipples **(c)** more darkening of the areola and appearance of a secondary areola.

(2) Progesterone : This causes development and growth of the secretory alveoli (acini) provided the gland is primed (i.e. prepared) by estrogens (page 131). However, this effect is apparent only during pregnancy

because it requires a relatively high concentration of progesterone. *During pregnancy, full development of the breasts occurs* by the effect of the high blood levels of *estrogen, progesterone, prolactin, hCS and possibly also hCG* (page 137).

(3) Prolactin : This stimulates milk secretion from the mammary glands that are *primed (prepared) by estrogen & progesterone*. During pregnancy, it is secreted in steadily increasing amounts from the 5th month till full term *under effect of the high estrogen blood level* (which directly stimulate the mammatropes). However, *estrogen also blocks the prolactin receptors in the mammary glands, thus preventing its milk secretion effect*. Prolactin is also secreted as a result of suckling (see below).

****** Because of the action of estrogen on the prolactin receptors in the mammary glands, *women who do not wish to nurse their babies are given regular doses of estrogen to stop lactation*.

(4) hCS : This is secreted by the placenta (page 140), and its secretion increases steadily from the 5th month till full term (like prolactin). However, it is a weaker stimulant for milk secretion than prolactin.

(5) Oxytocin : This causes milk ejection by stimulating contraction of the myoepithelial cells (page 31) that line the walls of the mammary ducts (which squeezes the preformed milk outwards through the nipples). Oxytocin secretion is produced as a result of the suckling reflex as well as in response to many emotional stimuli and conditioned reflexes (see below).

(6) Other hormones : The glucocorticoids, growth hormone and thyroxine are required to maintain the mammary functions produced by the other specific hormones discussed above.

INITIATION AND MAINTENANCE OF LACTATION AFTER LABOR

Absence of lactation during pregnancy is due to inhibition of the action of prolactin by the high blood estrogen level (see above). However, *after delivery of the baby and expulsion of the placenta, the sharp drop in the circulating estrogen blood level initiates lactation*.

Immediately after labor, the mammary glands secrete only a few ml of a fluid called **colostrum** (which contains a greater amount of proteins, but smaller amounts of lactose and fats than those present in milk), and it takes 1-3 days for the milk to "come in" instead of colostrum.

After delivery, prolactin secretion is decreased due to drop of the plasma estrogen level, so its plasma level decreases to the nonpregnant level in about 8 days. However, in lactating women the plasma prolactin level increases again because its secretion will be stimulated as a result

of the **suckling reflex** (figure 13). This reflex is initiated by suckling and is essential for maintenance of the process of lactation (i.e. milk secretion and ejection) because it *results in increasing the secretion of both prolactin and oxytocin* (page 32) by the following mechanisms :

1- Impulses initiated by touching the nipple are transmitted by afferent nerve fibres to the spinal cord then up to the hypothalamus where they inhibit the release of PIH (the prolactin inhibiting hormone). This stimulates secretion of prolactin from the anterior pituitary gland which induces milk secretion (= **milk secretion reflex**).

2- Impulses initiated by touching the nipple are similarly transmitted by afferent nerve fibres to the hypothalamus where they stimulate certain hypothalamic nuclei (particularly the *paraventricular nucleus*). Signals from these nuclei are then transmitted via the *hypothalamo-hypophyseal tract* to the neurohypophysis leading to release of oxytocin which causes milk ejection (= **milk ejection or letting reflex**).

****** *The effectiveness of these reflexes declines after 3 months of lactation, which leads to drop of the prolactin blood level. However, milk secretion will still occur with plasma prolactin levels that are in the normal range.*

****** Milk ejection can also occur as a result of **conditioned reflexes** e.g. when a mother hears her baby crying (or even just thinks at him), milk ejection may spontaneously occur as a result of oxytocin release from the posterior pituitary gland.

****** *The hypothalamic control on the release of both prolactin and oxytocin explains the lactation disturbances that might occur in emotions and the various psychological and stressful conditions.*

Effect of lactation on the menstrual cycles

In non-lactating women, *menstruation usually returns 6 weeks after delivery*. However, *lactation prevents the menstrual cycles during the first 6 - 7 months after delivery* (and 50% of lactating women do not ovulate as long as they are nursing their babies) because *lactation stimulates prolactin secretion which (a) Inhibits release of the GnRH and its effects on the anterior pituitary gland (b) Antagonizes the actions of the GTHs on the ovaries*. For this reason, **lactation can be used as a method of contraception** (page 128) but it is not a reliable method due to drop of the prolactin blood level after continuous lactation for about 3 months (see above). Also about **50% of the sex cycles in the first 6 months after return of menses are normally anovulatory** (page 127).

PROLACTIN

Prolactin (= mamotropin or lactogenic hormone) is secreted by the *mammotrope (lactotrope) cells of the anterior pituitary gland*. It is a polypeptide (consisting of 199 amino acids) which is structurally *similar to the growth hormone and hCS*, and its normal plasma concentration is about 5 ng/ml in males and 8 ng/ml in females. *Structurally similar prolactins are also secreted by the placenta and endometrium.*

Functions (actions) of prolactin

1- Together with other hormones (specially estrogens), it shares in the *development of mammary glands at puberty and during pregnancy*.

2- After labor, it initiates *lactogenesis* (secretion of milk from the mammary glands that are primed (prepared) by estrogen and progesterone). Lactogenesis is inhibited during pregnancy by the high blood estrogen level

3. Its function in males is unknown. However, **hyperprolactinemia in males causes hypogonadism and impotence** probably because prolactin inhibits secretion of the GnRH (page 146).

4. It prevents ovulation and produces amenorrhea e.g. during lactation (page 146) so **cases of hyperprolactinemia in women are characterized by galactorrhea (= increased milk secretion) that is associated with amenorrhea.**

Regulation (control) of prolactin secretion

(1) **Hypothalamic control** : The secretion of prolactin is controlled by the following 3 *hypophysiotropic hormones* that are secreted by the hypothalamus :

- a. A prolactin-releasing hormone (PRH).
- b. A prolactin-inhibiting hormone (PIH).
- c. TRH (which stimulates secretion of both TSH and prolactin, and some authors believe that **TRH is itself the PRH**).

In normal conditions, the inherent activity of the mammotrope cells (which secrete prolactin) is tonically inhibited, which indicates that the *effect of PIH normally overbalances the effects of PRH and TRH* . For this reason, it was found that section of the pituitary stalk leads to temporary elevation of the blood prolactin level (page 15).

****** The relation between the prolactin blood level and the hypothalamic hormones which affect its secretion is controlled by a **negative feedback mechanism** that aims at keeping the prolactin blood level constant. It occurs as follows : Rise of the prolactin blood level stimulates secretion of PIH, which inhibits prolactin secretion, thus its blood level decreases. An opposite effect occurs if the prolactin blood level falls.

(2) Effect of drugs : It was found that the **PIH is chemically dopamine**. Accordingly, the drugs that mimic dopamine (e.g. L-Dopa) or stimulate the dopamine receptors (e.g. bromocriptine and apomorphine) decrease prolactin secretion, whereas those which block the dopamine receptors (as phenothiazines e.g. chlorpromazine) increase prolactin secretion.

****** Like most hormones, the secretion of prolactin shows a **circadian rhythm**, being highest in the early morning and lowest in the evening.

(3) Effect of pregnancy : Prolactin secretion is ***progressively increased during pregnancy***, starting from the 5th month and reaching a peak at full term. This effect is produced by *the high blood estrogen level* although this also blocks the effect of prolactin on the mammary glands (page 145).

(4) Effect of sleep : The plasma prolactin level ***rises after the onset of sleep and persists throughout the sleep period***. The significance of this rise of the prolactin level during sleep and its mechanism are unknown.

(5) Effects of other factors : In humans, prolactin secretion is stimulated during exercise and on exposure to surgical and psychologic stresses (the significance of which is unknown), as well as by tactile stimulation of the nipples (page 32) through the suckling reflex (figure 13).

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